PCT/KR 02/01901

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APPLICATION NUMBER: *10/087,443*
FILING DATE: *March 01, 2002*

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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	37058-0008 P1
First Inventor	KAHN, Michael
Title	Reverse-Turn Mimetics and Method Relating Thereto
Express Mail Label No.	EL 912433445 US

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. ☐ Fee Transmittal Form (e.g., PTO/SB/17) *(Submit an original and a duplicate for fee processing)*
2. ☐ Applicant claims small entity status. See 37 CFR 1.27
3. ☒ Specification [Total Pages 75] *(preferred arrangement set forth below)*
   - Descriptive title of the Invention
   - Cross Reference to Related Applications
   - Statement Regarding Fed sponsored R & D
   - Reference to sequence listing, a table, or a computer program listing appendix
   - Background of the Invention
   - Brief Summary of the Invention
   - Brief Description of the Drawings *(if filed)*
   - Detailed Description
   - Claim(s)
   - Abstract of the Disclosure
4. ☒ Drawing(s) *(35 U.S.C. 113)* [Total Sheets 1]
5. Oath or Declaration [Total Pages]
   a. ☐ Newly executed (original or copy)
   b. ☐ Copy from a prior application (37 CFR 1.63 (d)) *(for continuation/divisional with Box 18 completed)*
      i. ☐ DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).
6. ☐ Application Data Sheet. See 37 CFR 1.76
7. ☐ CD-ROM or CD-R in duplicate, large table or Computer Program *(Appendix)*
8. Nucleotide and/or Amino Acid Sequence Submission *(if applicable, all necessary)*
   a. ☐ Computer Readable Form (CRF)
   b. Specification Sequence Listing on:
      i. ☐ CD-ROM or CD-R (2 copies); or
      ii. ☐ paper
   c. ☐ Statements verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

9. ☐ Assignment Papers (cover sheet & document(s))
10. ☐ 37 CFR 3.73(b) Statement *(when there is an assignee)* ☐ Power of Attorney
11. ☐ English Translation Document *(if applicable)*
12. ☐ Information Disclosure Statement (IDS)/PTO-1449 ☐ Copies of IDS Citations
13. ☐ Preliminary Amendment
14. ☒ Return Receipt Postcard (MPEP 503) *(Should be specifically itemized)*
15. ☐ Certified Copy of Priority Document(s) *(if foreign priority is claimed)*
16. ☒ Nonpublication Request under 35 U.S.C. 122 (b)(2)(B)(i). Applicant must attach form PTO/SB/35 or its equivalent.
17. ☒ Other: Information Sheet

18. If a CONTINUING APPLICATION, *check appropriate box, and supply the requisite information below and in a preliminary amendment, or in an Application Data Sheet under 37 CFR 1.76:*

☐ Continuation ☐ Divisional ☒ Continuation-in-part (CIP) of prior application No: 09 / 976,470

Prior application information: Examiner Not yet assigned Group Art Unit 1645

For CONTINUATION OR DIVISIONAL APPS only: The entire disclosure of the prior application, from which an oath or declaration is supplied under Box 5b, is considered a part of the disclosure of the accompanying continuation or divisional application and is hereby incorporated by reference. The incorporation can only be relied upon when a portion has been inadvertently omitted from the submitted application parts.

19. CORRESPONDENCE ADDRESS

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Signature	[signature]	Date	March 1, 2002

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Washington, DC 20231

Attorney Docket No: 37058-0008 P1

INFORMATION SHEET

TITLE

REVERSE-TURN MIMETICS AND METHOD RELATING THERETO

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NONPUBLICATION REQUEST UNDER 35 U.S.C. 122(b)(2)(B)(i)		
	First Named Inventor	KAHN, Michael
	Title	Reverse-Turn Mimetics and Method Relating Thereto
	Atty Docket Number	37058-0008 P1

I hereby certify that the invention disclosed in the attached application **has not and will not be** the subject of an application filed in another country, or under a multilateral agreement, that requires publication at eighteen months after filing.

I hereby request that the attached application not be published under 35 U.S.C. 122(b).

March 1, 2002
Date

Signature

Stacy Ann Hegle
Agent for Applicants
Reg. No. 50,687

This request must be signed in compliance with 37 CFR 1.33(b) and submitted with the application upon filing.

Applicant may rescind this nonpublication request at any time. If applicant rescinds a request that an application not be published under 35 U.S.C. 122(b), the application will be scheduled for publication at eighteen months from the earliest claimed filing date for which a benefit is claimed.

If applicant subsequently files an application directed to the invention disclosed in the attached application in another country, or under a multilateral international agreement, that requires publication of applications eighteen months after filing, the applicant must notify the United States Patent and Trademark Office of such filing within forty-five (45) days after the date of the filing of such foreign or international application. **Failure to do so will result in abandonment of this application (35 U.S.C. 122(b)(2)(B)(iii)).**

REVERSE-TURN MIMETICS AND METHOD RELATING THERETO

CROSS REFERENCE TO PARENT APPLICATION

[0001] This application is a continuation-in-part of U.S. patent application Ser. No. 09/976,470, filed October 12, 2001, the entire disclosure of which is incorporated by reference.

TECHNICAL FIELD

[0002] The present invention relates generally to reverse-turn mimetic structures and to a chemical library relating thereto.

BACKGROUND OF THE INVENTION

[0003] Random screening of molecules for possible activity as therapeutic agents has occurred for many years and resulted in a number of important drug discoveries. While advances in molecular biology and computational chemistry have led to increased interest in what has been termed "rational drug design", such techniques have not proven as fast or reliable as initially predicted. Thus, in recent years there has been a renewed interest and return to random drug screening. To this end, particular strides having been made in new technologies based on the development of combinatorial chemistry libraries, and the screening of such libraries in search for biologically active members.

[0004] In general, combinatorial chemistry libraries are simply a collection of molecules. Such libraries vary by the chemical species within the library, as well as the

methods employed to both generate the library members and identify which members interact with biological targets of interest. While this field is still young, methods for generating and screening libraries have already become quite diverse and sophisticated. For example, a recent review of various combinatorial chemical libraries has identified a number of such techniques (Dolle, *J. Com. Chem.*, 2(3): 383-433, 2000), including the use of both tagged and untagged library members (Janda, *Proc. Natl. Acad. Sci. USA* 91:10779-10785, 1994).

[0005] Initially, combinatorial chemistry libraries were generally limited to members of peptide or nucleotide origin. To this end, the techniques of Houghten et al. illustrate an example of what is termed a "dual-defined iterative" method to assemble soluble combinatorial peptide libraries via split synthesis techniques (*Nature* (London) 354:84-86, 1991; *Biotechniques* 13:412-421, 1992; Bioorg. *Med. Chem. Lett.* 3:405-412, 1993). By this technique, soluble peptide libraries containing tens of millions of members have been obtained. Such libraries have been shown to be effective in the identification of opioid peptides, such as methionine- and leucine-enkephalin (Dooley and Houghten, *Life Sci.* 52, 1509-1517, 1993), and a N-acylated peptide library has been used to identify acetalins, which are potent opioid antagonists (Dooley et al., *Proc. Natl. Acad. Sci. USA* 90:10811-10815, 1993. More recently, an all D-amino acid opioid peptide library has been constructed and screened for analgesic activity against the mu ("μ ") opioid receptor (Dooley et al, *Science* 266:2019-2022, 1994).

[0006] While combinatorial libraries containing members of peptide and nucleotide origin are of significant value, there is still a need in the art for libraries containing members of different origin. For example, traditional peptide libraries to a large extent merely vary the amino acid sequence to generate library members. While it

is well recognized that the secondary structures of peptides are important to biological activity, such peptide libraries do not impart a constrained secondary structure to its library members.

[0007] To this end, some researchers have cyclized peptides with disulfide bridges in an attempt to provide a more constrained secondary structure (Tumelty et al., *J. Chem. Soc.* 1067-68, 1994; Eichler et al., *Peptide Res.* 7:300-306, 1994). However, such cyclized peptides are generally still quite flexible and are poorly bioavailable, and thus have met with only limited success.

[0008] More recently, non-peptide compounds have been developed which more closely mimic the secondary structure of reverse-turns found in biologically active proteins or peptides. For example, U.S. Pat. No. 5,440,013 to Kahn and published PCT WO94/03494, PCT WO01/00210A1, and PCT WO01/16135A2 to Kahn these disclose conformationally constrained, non-peptidic compounds, which mimic the three-dimensional structure of reverse-turns.

[0009] While significant advances have been made in the synthesis and identification of conformationally constrained, reverse-turn mimetics, there remains a need in the art for small molecules, which mimic the secondary structure of peptides. There has been also a need in the art for libraries containing such members, as well as techniques for synthesizing and screening the library members against targets of interest, particularly biological targets, to identify bioactive library members. For example U.S. Pat. No. 5,929,237 and its continuation-in-part U.S. Pat. No. 6,013,458 to Kahn also discloses conformationally constrained compounds which mimic the secondary structure of reverse-turn regions of biologically active peptides and proteins.

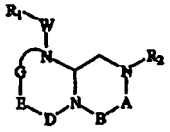
[0010] The present invention also fulfills these needs, and provides further

related advantages by providing confomationally constrained compounds which mimic the secondary structure of reverse-turn regions of biologically active peptides and proteins.

SUMMARY OF THE INVENTION

[0011] In brief, the present invention is directed to another type of conformationally constrained compounds, which mimic the secondary structure of reverse-turn regions of biologically active peptides and proteins. This invention also discloses libraries containing such compounds, as well as the synthesis and screening thereof.

[0012] The compounds of the present invention have the following general formula (I):

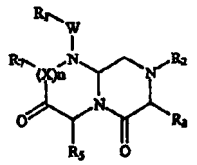


(I)

wherein A is -(CHR_3)- or -(C=O)-, B is -(CHR_4)- or -(C=O)-, D is –(CHR_5)- or –(C=O)-, E is –(ZR_6)- or -(C=O)-, G is –(XR_7)$_n$-, -(CHR_7)-(NR_8)-, -(C=O)-(XR_9)-, or -(C=O)- , W is –Y(C=O)-, -(C=O)NH-, -(SO_2)- or nothing, Y is oxygen or sulfur, X and Z is independently nitrogen or CH, n=0 or 1; and R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8 and R_9 are the same or different and independently selected from an amino acid side chain moiety or derivative thereof, the remainder of the molecule, a linker and a solid support, and stereoisomers thereof.

[0013] In the embodiment wherein A is –(CHR_3)-, B is –(C=O)-, D is –(CHR_5)-, E is –(C=O)-, and G is –(XR_7)$_n$-, the compounds of this invention have the following

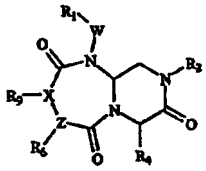
formula (II):



(II)

Wherein W, Y and n are as defined above, and R_1, R_2, R_3, R_5 and R_7 are as defined in the following detailed description.

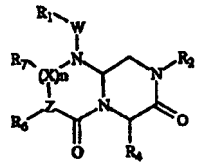
[0014] In the embodiment wherein A is –(C=O)-, B is -(CHR$_4$) -, D is –(C=O)-, E is –(ZR$_6$)-, and G is –(C=O)-(XR$_9$)-, the compounds of this invention have the following formula (III):



(III)

wherein W, Y and n are as defined above, Z is nitrogen or CH (when Z is CH, then X is nitrogen), and R_1, R_2, R_4, R_6 and R_9 are as defined in the following detailed description.

[0015] In the embodiment wherein A is –(C=O)-, B is –(CHR$_4$)-, D is –(C=O)-, E is –(ZR$_6$)-, and G is (XR$_7$)$_n$-, the compounds of this invention have the following general formula (IV):



(IV)

wherein W, Y and n are as defined above, Z is nitrogen or CH (when Z is nitrogen, then n is zero, and when Z is CH, then X is nitrogen and n is not zero), and R_1, R_2, R_4, R_6 and

R_7, are as defined in the following detailed description.

[0016] The present invention is also directed to libraries containing compounds of formula (I) above, as well as methods for synthesizing such libraries and methods for screening the same to identify biologically active compounds. Compositions containing a compound of this invention in combination with a pharmaceutically acceptable carrier or diluent are also disclosed.

[0017] Especially, the present invention relates pharmaceutical compositions containing thereof for treating disorders including cancers which are associated with Wnt signaling pathway. It further relates to methods for treating disorders including cancer which are associated with Wnt signaling pathway.

[0018] These and other aspects of this invention will be apparent upon reference to the attached figures and following detailed description. To this end, various references are set forth herein, which describe in more detail certain procedures, compounds and/or compositions, and are incorporated by reference in their entirety.

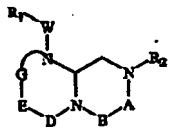
BRIFF DESCRIPTION OF THE DRAWING

[0019] Fig. 1. Shows a graph for the measurement of IC50 of a compound of the present invention for SW480 cells, wherein Cell growth inhibition on SW480 cells is measured at various concentrations of the compound prepared in Example 4 in order to obtain the IC_{50} value. Specifically, the degree of inhibition in firefly and renilla luciferase activities by said test compound was determined. As a result, IC_{50} of said test compound against SW480 cell growth was found to be about 8.070. Detailed procedures are the same as disclosed in Example 6.

DETAILED DESCRIPTION OF THE INVENTION

[0020] The present invention is directed to conformationally constrained compounds which mimic the secondary structure of reverse-turn regions of biological peptide and proteins (also referred to herein as "reverse-turn mimetics" and chemical libraries relating thereto. The reverse-turn mimetic structures of the present invention are useful as bioactive agents, including (but not limited to) use as diagnostic, prophylactic and/or therapeutic agents. The reverse-turn mimetic structure libraries of this invention are useful in the identification of such bioactive agents. In the practice of the present invention, the libraries may contain from tens to hundreds to thousands (or greater) of individual reverse-turn structures (also referred to herein as "members").

[0021] In one aspect of the present invention, a reverse-turn mimetic structure is disclosed having the following formula (I):



(I)

wherein A is -(CHR_3)- or -(C=O)-, B is -(CHR_4)- or -(C=O)-, D is –(CHR_5)- or –(C=O)-, E is –(ZR_6)- or -(C=O)-, G is –(XR_7)$_n$-, -(CHR_7)-(NR_8)-, -(C=O)-(XR_9)-, or -(C=O)- , W is –Y(C=O)-, -(C=O)NH- , -(SO_2)- or nothing, Y is oxygen or sulfur, X and Z is independently nitrogen or CH, n=0 or 1; and R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8 and R_9 are the same or different and independently selected from an amino acid side chain moiety or derivative thereof, the remainder of the molecule, a linker and a solid support, and stereoisomers thereof.

[0022] More specifically, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8 and R_9 are independently selected from the group consisting of aminoC_{2-5}alkyl, guanidinoC_{2-5}alkyl, C_1-

$_{4}$alkylguanidinoC_{2-5}alkyl, diC_{1-4}alkylguanidino-C_{2-5}alkyl, amidinoC_{2-5}alkyl,C_{1-4}alkylamidinoC_{2-5}alkyl, diC_{1-4}alkylamidinoC_{2-5}alkyl, C_{1-3}alkoxy, Phenyl, substituted phenyl(where the substituents are independently selected from one or more of amino, amidino, guanidine, hydrazine, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl, or hydroxyl), benzyl, substituted benzyl (where the substituents on the benzyl are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl, or hydroxyl), naphthyl, substituted naphthyl(where the substituents are independently selected from one or more of amino, amidino, guanidine, hydrazine, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl, or hydroxyl), bis-phenyl methyl, substituted bis-phenyl methyl(where the substituents are independently selected from one or more of amino, amidino, guanidine, hydrazine, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl, or hydroxyl), pyridyl, substituted pyridyl, (where the substituents are independently selected from one or more of amino amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl, or hydroxyl), pyridylC_{1-4}alkyl, substituted pyridylC_{1-4}alkyl (where the pyridine substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl, or hydroxyl), pyrimidylC_{1-4}alkyl, substituted pyrimidylC_{1-4}alkyl (where the pyrimidine substituents are independently selected from one or more of amino, amidino,

guanidine, hydrazine, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy or nitro, carboxy, cyano, sulfuryl, or hydroxyl), triazin-2-yl-C_{1-4}alkyl, substituted triazin-2-yl-C_{1-4}alkyl (where the triazine substituents are independently selected from one or more of amino, amidino, guanidine, hydrazine, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl, or hydroxyl), imidazoC_{1-4}alkyl, substituted imidazol C_{1-4}alkl (where the imidazole substituents are independently selected from one or more of amino, amidino, guanidine, hydrazine, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl, or hydroxyl), imidazolinylC_{1-4}alkyl, N-amidinopiperazinyl-N-C_{0-4}alkyl, hydroxyC_{2-5}alkyl, C_{1-5}alkylaminoC_{2-5}alkyl, hydroxyC_{2-5}alkyl, C_{1-5}alkylaminoC_{2-5}alkyl, C_{1-5}dialkylaminoC_{2-5}alkyl, N-amidinopiperidinylC_{1-4}alkyl and 4-aminocyclohexylC_{0-2}alkyl.

[0023] In one embodiment, R_1, R_2, R_6 of B, and R_7, R_8 and R_9 of G are the same or different and represent the remainder of the compound, and R_3 of A, R_4 of B or R_5 of D is selected from an amino acid side chain moiety or derivative thereof. As used herein, the term "remainder of the compound" means any moiety, agent, compound, support, molecule, linker, amino acid, peptide or protein covalently attached to the reverse-turn mimetic structure at R_1, R_2, R_5, R_6, R_7, R_8 and/or R_9 positions. This term also includes amino acid side chain moieties and derivatives thereof.

[0024] As used herein, the term "amino acid side chain moiety" represents any amino acid side chain moiety present in naturally occurring proteins including (but not limited to) the naturally occurring amino acid side chain moieties identified in Table 1. Other naturally occurring amino acid side chain moieties of this invention include (but

are not limited to) the side chain moieties of 3,5-dibromotyrosine, 3,5-diiodotyrosine, hydroxylysine, γ-carboxyglutamate, phosphotyrosine and phosphoserine. In addition, glycosylated amino acid side chains may also be used in the practice of this invention, including (but not limited to) glycosylated threonine, serine and asparagine.

TABLE 1

Amino Acid Side Chain Moieties

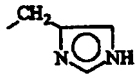
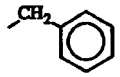
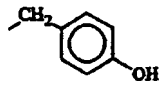
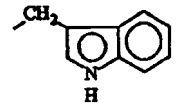
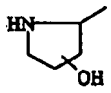
Amino Acid Side Chain Moiety	Amino Acid
–H	Glycine
$-CH_3$	Alanine
$-CH(CH_3)_2$	Valine
$-CH_2\ CH(CH_3)_2$	Leucine
$-CH(CH_3)CH_2\ CH_3$	Isoleucine
$-(CH_2)_4NH_3^+$	Lysine
$-(CH_2)_3NHC(NH_2)NH_2^+$	Arginine
	Histidine
$-CH_2COO^-$	Aspartic acid
$-CH_2CH_2COO^-$	Glutamic acid
$-CH_2CONH_2$	Asparagine
$-CH_2CH_2CONH_2$	Glutamine
	Phenylalanine
	Tyrosine
	Tryptophan
$-CH_2SH$	Cysteine

TABLE 1 (cont.)

Amino Acid Side Chain Moieties	
Amino Acid Side Chain Moiety	Amino Acid
$-CH_2CH_2SCH_3$	Methionine
$-CH_2OH$	Serine
$-CH(OH)CH_3$	Threonine
	Proline
	Hydroxyproline

[0025] In addition to naturally occurring amino acid side chain moieties, the amino acid side chain moieties of the present invention also include various derivatives thereof. As used herein, a "derivative" of an amino acid side chain moiety includes modifications and/or variations to naturally occurring amino acid side chain moieties. For example, the amino acid side chain moieties of alanine, valine, leucine, isoleucine and phenylalanine may generally be classified as lower chain alkyl, aryl, or arylalkyl moieties. Derivatives of amino acid side chain moieties include other straight chain or branched, cyclic or noncyclic, substituted or unsubstituted, saturated or unsaturated lower chain alkyl, aryl or arylalkyl moieties.

[0026] As used herein, "lower chain alkyl moieties" contain from 1-12 carbon atoms, "lower chain aryl moieties" contain from 6-12 carbon atoms and "lower chain aralkyl moieties" contain from 7-12 carbon atoms. Thus, in one embodiment, the amino acid side chain derivative is selected from a C_{1-12} alkyl, a C_{6-12} aryl and a C_{7-12} arylalkyl, and in a more preferred embodiment, from a C_{1-7} alkyl, a C_{6-10} aryl and a C_{7-11} arylalkyl.

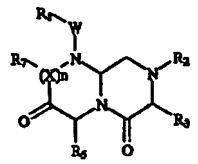
[0027] Amino side chain derivatives of this invention further include substituted

derivatives of lower chain alkyl, aryl, and arylalkyl moieties, wherein the substituent is selected from (but are not limited to) one or more of the following chemical moieties: -OH, -OR, -COOH, -COOR, -$CONH_2$, -NH_2, -NHR, -NRR, -SH, -SR, -SO_2R, -SO_2H, -SOR and halogen (including F, Cl, Br and I), wherein each occurrence of R is independently selected from straight chain or branched, cyclic or noncyclic, substituted or unsubstituted, saturated or unsaturated lower chain alkyl, aryl and aralkyl moieties. Moreover, cyclic lower chain alkyl, aryl and arylalkyl moieties of this invention include naphthalene, as well as heterocyclic compounds such as thiophene, pyrrole, furan, imidazole, oxazole, thiazole, pyrazole, 3-pyrroline, pyrrolidine, pyridine, pyrimidine, purine, quinoline, isoquinoline and carbazole. Amino acid side chain derivatives further include heteroalkyl derivatives of the alkyl portion of the lower chain alkyl and aralkyl moieties, including (but not limited to) alkyl and aralkyl phosphonates and silanes.

[0028] Representative R_1, R_2, R_5, R_6, R_7, R_8 and R_9 moieties specifically include (but are not limited to) -OH, -OR, -COR, -COOR, -$CONH_2$, -CONR, -CONRR, -NH_2, -NHR, -NRR, -SO_2R and -COSR, wherein each occurrence of R is as defined above.

[0029] In a further embodiment, and in addition to being an amino acid side chain moiety or derivative thereof (or the remainder of the compound in the case of R_1, R_2, R_5, R_6, R_7, R_8 and R_9), R_1, R_2, R_5, R_6, R_7, R_8 or R_9may be a linker facilitating the linkage of the compound to another moiety or compound. For example, the compounds of this invention may be linked to one or more known compounds, such as biotin, for use in diagnostic or screening assay. Furthermore, R_1, R_2, R_5, R_6, R_7, R_8 or R_9 may be a linker joining the compound to a solid support (such as a support used in solid phase peptide synthesis) or alternatively, may be the support itself. In this embodiment, linkage to another moiety or compound, or to a solid support, is preferable at the R_1, R_2,

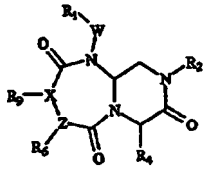
R_7 or R_8 position, and more preferably at the R_1 or R_2 position. In the embodiment wherein A is $-(CHR_3)-$, B is $-(C=O)-$, D is $-(CHR_5)-$, E is $-(C=O)-$, G is $-(XR_7)_n-$, the reverse turn mimetic compound of this invention have the following formula (II):



(II)

wherein R_1, R_2, R_3, R_5, R_7, W, X and n are as defined above. In a preferred embodiment, R_1, R_2 and R_7 represent the remainder of the compound, and R_3 or R_5 is selected from an amino acid side chain moiety.

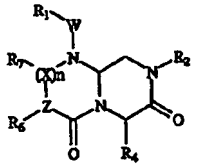
[0030] In the embodiment wherein A is $-(C=O)-$, B is $-(CHR_4)-$, D is $-(C=O)-$, E is $-(ZR_6)-$, G is $-(C=O)-(XR_9)-$, the reverse turn mimetic compound of this invention have the following general formula (III):



(III)

wherein R_1, R_2, R_4, R_6, R_9, W and X are as defined above, Z is nitrogen or CH (when Z is CH, then X is nitrogen). In a preferred embodiment, R_1, R_2 , R_6 and R_9 represent the remainder of the compound, and R_4 is selected from an amino acid side chain moiety.

[0031] In a more specific embodiment wherein A is $-(C=O)-$, B is $-(CHR_4)-$, D is $-(C=O)-$, E is $-(ZR_6)-$, G is $(XR_7)_n-$, the reverse turn mimetic compound of this invention have the following formula (IV):



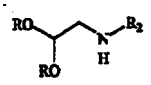
(IV)

wherein R_1, R_2, R_4, R_6, R_7, W, X and n are as defined above, and Z is nitrogen or CH (when Z is nitrogen, then n is zero, and when Z is CH, then X is nitrogen and n is not zero). In a preferred embodiment, R_1, R_2, R_6 and R_7 represent the remainder of the compound, and R_4 is selected from an amino acid side chain moiety. In this case, R_6 or R_7 may be selected from an amino acid side chain moiety when Z and X are CH, respectively.

[0032] The reverse-turn mimetic structures of the present invention may be prepared by utilizing appropriate starting component molecules (hereinafter referred to as "component pieces"). Briefly, in the synthesis of reverse-turn mimetic structures having formula (II), first and second component pieces are coupled to form a combined first-second intermediate, if necessary, third and/or fourth component pieces are coupled to form a combined third-fourth intermediate (or, if commercially available, a single third intermediate may be used), the combined first-second intermediate and third-fourth intermediate (or third intermediate) are then coupled to provide a first-second-third-fourth intermediate (or first-second-third intermediate) which is cyclized to yield the reverse-turn mimetic structures of this invention. Alternatively, the reverse-turn mimetic structures of formula (II) may be prepared by sequential coupling of the individual component pieces either stepwise in solution or by solid phase synthesis as commonly practiced in solid phase peptide synthesis.

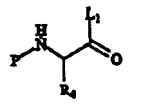
[0033] Within the context of the present invention, a "first component piece" has

the following formula S1:


(S1)

wherein R_2 as defined above, and R is a protective group suitable for use in peptide synthesis. Suitable R groups include alkyl groups and, in a preferred embodiment, R is a methyl group. Such first component pieces may be readily synthesized by reductive amination by displacement from $CH(OR)_2$-CH_2-Hal (wherein Hal means a halogen atom) H_2N-R_2.

[0034] A "second component piece" of this invention has the following formula S2:

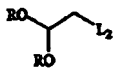

(S2)

where L_1 is carboxyl-activation group such as halogen atom, R_4 is as defined above, and P is an amino protective group suitable for use in peptide synthesis. Preferred protective groups include t-butyl dimethylsilyl (TBDMS), BOC, FMOC, and Alloc(allyloxycarbonyl). When L is –C(O)NHR, -NHR may be an carboxyl protective group. N-Protected amino acids are commercially available. For example, FMOC amino acids are available from a variety of sources. The conversion of these compounds to the second component pieces of this invention may be readily achieved by activation of the carboxylic acid group of the N-protected amino acid. Suitable activated carboxylic acid groups include acid halides where X is a halide such as chloride or bromide, acid anhydrides where X is an acyl group such as acetyl, reactive esters such as an N-hydroxysuccinimide esters and pentafluorophenyl esters, and other activated

intermediates such as the active intermediate formed in a coupling reaction using a carbodiimide such as dicyclohexylcarbodiimide (DCC).

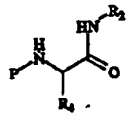
[0035] In the case of the azido derivative of an amino acid serving as the second component piece, such compounds may be prepared from the corresponding amino acid by the reaction disclosed by Zaloom et al. (*J. Org. Chem.* 46:5173-76, 1981).

[0036] Alternatively, the first piece of the invention may have the following formula S1':



(S1')

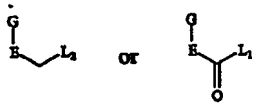
wherein R is as defined above and L_2 is a leaving group such as halogen atom or tosyl group, and the second piece of the invention may have the following formula S2':



(S2')

wherein R_2, R_3 and P are as defined above.

[0037] A "third component piece" of this invention has the following formula S3a or S3b:



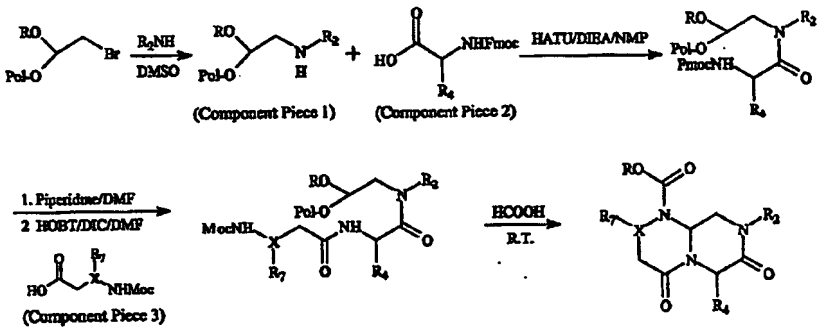
(S3a) (S3b)

where G, E, L_1 and L_2 are as defined above. Suitable third component pieces are commercially available from a variety of sources or can be prepared by any known method in organic chemistry.

[0038] More specifically, the reverse-turn mimetic structures of this invention of formula (II) are synthesized by reacting a first component piece with a second

component piece to yield a combined first-second intermediate, followed by either reacting the combined first-second intermediate with third component pieces sequentially to provide a combined first-second-third-fourth intermediate, and then cyclizing this intermediate to yield the reverse-turn mimetic structure.

[0039] The general synthesis of a reverse-turn having structure I' may be synthesized by the following technique. A first component piece 1 is coupled with a second component piece 2 by using coupling reagent such as phosgene to yield, after N-deprotection, a combined first-second intermediate 1-2 as illustrated below:



wherein, R, R_2, R_4, R7, Fmoc, Moc and X are as defined above, and Pol represents a polymeric support.

[0040] The syntheses of representative component pieces of this invention are described in Preparation Examples and working Examples.

[0041] The reverse-turn mimetic structures of formula (III) and (IV) may be made by techniques analogous to the modular component synthesis disclosed above, but with appropriate modifications to the component pieces.

[0042] As mentioned above, the reverse-turn mimetics of USP 6,013,458 to Kahn, et al. are useful as bioactive agents, such as diagnostic, prophylactic, and

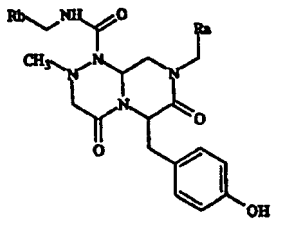
therapeutic agents. The opiate receptor binding activity of representative reverse-turn mimetics is presented in Example 9 of said US 6,013,458, wherein the reverse-turn mimetics of this invention were found to effectively inhibit the binding of a radiolabeled enkephalin derivative to the δ and μ opiate receptors, of which data demonstrates the utility of these reverse-turn mimetics as receptor agonists and as potential analgesic agents.

[0043] The reverse-turn mimetic structures of the present invention will be useful as bioactive agents, such as diagnostic, prophylactic, and therapeutic agents.

[0044] Therefore, since the compounds according to the present invention are of reverse-turn mimetic structures, it may be useful for modulating a cell signaling transcription factor related peptides in a warm-blooded animal, comprising administering to the animal an effective amount of the compound of formula (I).

[0045] Further, the reverse-turn mimetic structures of the present invention may also be effective for inhibiting peptide binding to PTB domains in a warm-blooded animal; for modulating G protein coupled receptor (GPCR) and ion channel in a warm-blooded animal; for modulating cytokines in a warm-blooded animal.

[0046] Meanwhile, it has been found that the compounds of the formula (I), especially compounds of formula (VI) are effective for inhibiting or treating disorders modulated by Wnt-signaling pathway, such as cancer, especially colorectal cancer.



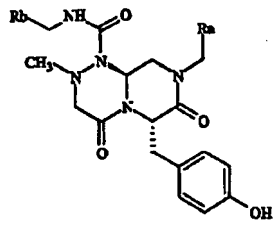
(VI)

wherein, R_a is a bicyclic aryl group having 8 to 11 ring members, which may have 1 to 3 heteroatoms selected from nitrogen, oxygen or sulfur, and R_b is a monocyclic aryl group having 5 to 7 ring members, which may have 1 to 2 heteroatoms selected from nitrogen, oxygen or sulfur, and aryl ring in the compound may have one or more substituents selected from a group consisting of halide, hydroxy, cyano, lower alkyl, and lower alkoxy group.

[0047] Therefore, it is an object of the present invention to provide a pharmaceutical composition comprising a safe and effective amount of the compound having general formula (VI) and pharmaceutically acceptable carrier, which can be used for treatment of disorders modulated by Wnt signaling pathway, especially by TCF4- β-catenin- CBP complex.

[0048] Further, the present invention is to provide a method for inhibiting the growth of tumor cells by using the above-described composition of the present invention; a method for inducing apoptosis of tumor cells by using the above-described composition of the present invention; a method for treating a disorder modulated by TCF4-β catenin-CBP complex by using the above-described composition of the present invention; and a method of treating cancer such as colorectal cancer by administering the composition of the present invention together with other anti-cancer agent such as 5-fluorouracil (5-FU).

[0049] In a preferred embodiment of the present invention, the compound of the present invention has a (6S,10R)-configuration as follows:



(VIa)

wherein R_a and R_b have the same meanings as defined above.

[0050] In another aspect of this invention, libraries containing reverse-turn mimetic structures of the present invention are disclosed. Once assembled, the libraries of the present invention may be screened to identify individual members having bioactivity. Such screening of the libraries for bioactive members may involve; for example, evaluating the binding activity of the members of the library or evaluating the effect the library members have on a functional assay. Screening is normally accomplished by contacting the library members (or a subset of library members) with a target of interest, such as, for example, an antibody, enzyme, receptor or cell line. Library members, which are capable of interacting with the target of interest, are referred to herein as "bioactive library members" or "bioactive mimetics". For example, a bioactive mimetic may be a library member which is capable of binding to an antibody or receptor, which is capable of inhibiting an enzyme, or which is capable of eliciting or antagonizing a functional response associated, for example, with a cell line. In other words, the screening of the libraries of the present invention determines which library members are capable of interacting with one or more biological targets of interest. Furthermore, when interaction does occur, the bioactive mimetic (or mimetics) may then be identified from the library members. The identification of a single (or limited number) of bioactive mimetic(s) from the library yields reverse-turn mimetic

structures which are themselves biologically active, and thus useful as diagnostic, prophylactic or therapeutic agents, and may further be used to significantly advance identification of lead compounds in these fields.

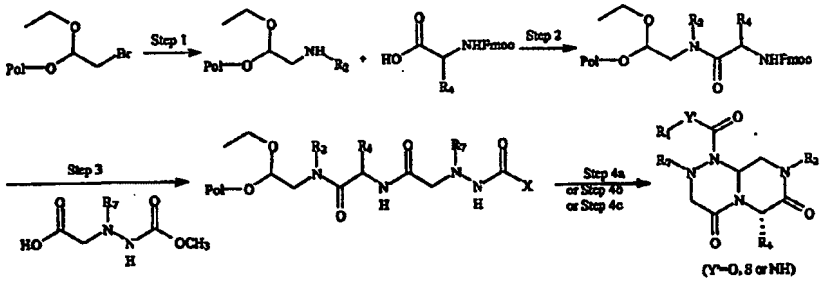
[0051] Synthesis of the peptide mimetics of the library of the present invention may be accomplished using known peptide synthesis techniques, in combination with the first, second and third component pieces of this invention. More specifically, any amino acid sequence may be added to the N-terminal and/or C-terminal of the conformationally constrained reverse-turn mimetic. To this end, the mimetics may be synthesized on a solid support (such as PAM resin) by known techniques (see, e.g., John M. Stewart and Janis D. Young, Solid Phase Peptide Synthesis, 1984, Pierce Chemical Comp., Rockford, Ill.) or on a silyl-linked resin by alcohol attachment (see Randolph et al., *J. Am Chem. Soc.* 117:5712-14, 1995).

[0052] In addition, a combination of both solution and solid phase synthesis techniques may be utilized to synthesize the peptide mimetics of this invention. For example, a solid support may be utilized to synthesize the linear peptide sequence up to the point that the conformationally constrained reverse-turn is added to the sequence. A suitable conformationally constrained reverse-turn mimetic structures which has been previously synthesized by solution synthesis techniques may then be added as the next "amino acid" to the solid phase synthesis (i.e., the conformationally constrained reverse-turn mimetic, which has both an N-terminus and a C-terminus, may be utilized as the next amino acid to be added to the linear peptide). Upon incorporation of the conformationally constrained reverse-turn mimetic structures into the sequence, additional amino acids may then be added to complete the peptide bound to the solid support. Alternatively, the linear N-terminus and C-terminus protected peptide

sequences may be synthesized on a solid support, removed from the support, and then coupled to the conformationally constrained reverse-turn mimetic structures in solution using known solution coupling techniques.

[0053] In another aspect of this invention, methods for constructing the libraries are disclosed. Traditional combinatorial chemistry techniques (see, e.g., Gallop et al., *J. Med. Chem.* 37:1233-1251, 1994) permit a vast number of compounds to be rapidly prepared by the sequential combination of reagents to a basic molecular scaffold. Combinatorial techniques have been used to construct peptide libraries derived from the naturally occurring amino acids. For example, by taking 20 mixtures of 20 suitably protected and different amino acids and coupling each with one of the 20 amino acids, a library of 400 (i.e., 20^2) dipeptides is created. Repeating the procedure seven times results in the preparation of a peptide library comprised of about 26 billion (i.e., 20^8) octapeptides.

[0054] Specifically, synthesis of the peptide mimetics of the library of the present invention may be accomplished using known peptide synthesis techniques, for example, the General Scheme of [4,4,0] Reverse-Turn Mimetic Library as follows:



[0055] Synthesis of the peptide mimetics of the libraries of the present invention was accomplished using FlexChem Reactor Block which has 96 well plate by known techniques. In the above scheme 'Pol' represents Bromoacetal resin(Advanced

ChemTech) and detailed procedure is illustrated bellow.

Step 1

[0056] The bromoacetal resin (37mg, 0.98 mmol/g) and a solution of R_2-amine in DMSO (1.4mL) were placed in 96 well Robbinns block (FlexChem). The reaction mixture was shaken at 60°C using rotating oven [robbins Scientific] for 12 hs. The resin was washed with DMF, MeOH, then DCM.

Step 2

[0057] A solution of commercial available FmocAminoAcids (4eq.), PyBob (4eq)., HOAt (4eq.), and DIEA (12 eq.) in DMF was added to the resin. After the reaction mixture was shaken for 12 hrs at room temperature, the resin was washed with DMF, MeOH, and then DCM.

Step 3

[0058] To the resin swollen by DMF before reaction was added 25% piperidine in DMF. After the reaction mixture was shaken for 30 min at room temperature. This deprotection step was repeated again and then washed with DMF, Methanol, then DCM. A solution of hydrazine acid (4 eq.), HOBt (4 eq.), and DIC (4 eq.) in DMF was added to the resin. After the reaction mixture was shaken for 12 hrs at room temperature, the resin was washed with DMF, MeOH, and then DCM.

Step 4a (In the case of hydrazine acid was Moc carbamate)

[0059] The resin was treated with formic acid (1.2 mL each well) for 18 hrs at room temperature. After the resin was removed by filtration, the filtrate was condensed under reduced pressure using SpeedVac [SAVANT] to give the product as oil. These products were diluted with 50% water/acetonitrile and then lyophilized after freezing.

Step 4b (In the case of Fmoc hydrazine acid to make Urea through isocynate)

[0060] To the resin swollen by DMF before reaction was added 25% piperidine in DMF. After the reaction mixture was shaken for 30 min at room temperature. This deprotection step was repeated again and then washed with DMF, Methanol, then DCM. To the resin swollen by DCM before reaction was added isocynate (5 eq.) in DCM. After the reaction mixture was shaken for 12 hrs at room temperature the resin was washed with DMF, MeOH, then DCM. The resin was treated with formic acid (1.2 mL each well) for 18 hrs at room temperature. After the resin was removed by filtration, the filtrate was condensed under reduced pressure using SpeedVac [SAVANT] to give the product as oil. These products were diluted with 50% water/acetonitrile and then lyophilized after freezing.

Step 4c (In the case of Fmoc-hydrazine acid to make Urea through active carbamate)

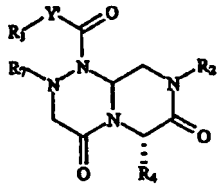
[0061] To the resin swollen by DMF before reaction was added 25% piperidine in DMF. After the reaction mixture was shaken for 30 min at room temperature. This deprotection step was repeated again and then washed with DMF, MeOH, then DCM. To the resin swollen by DCM before reaction was added p-nitrophenyl chloroformate (5 eq.), Diisopropyl ethylamine (5 eq.) in DCM. After the reaction mixture was shaken for 12 hrs at room temperature, the resin was washed with DMF, MeOH, then DCM. To the resin was added primary amines in DCM for 12 hrs at room temperature, the resin was washed with DMF, MeOH, then DCM. After reaction the resin was treated with formic acid (1.2 mL each well) for 18 hrs at room temperature. After the resin was removed by filtration, the filtrate was condensed under reduced pressure using SpeedVac[SAVANT] to give the product as oil. These products were diluted with 50%

water/acetonitrile and then lyophilized after freezing.

[0062] To generate these block libraries the key intermediate hydrazine acids were synthesized according to the procedure illustrated in Preparation Examples.

[0063] Table 2 shows a [4,4,0] Reverse turn mimetics library which can be prepared according to the present invention, of which representative preparation is given in Example 4

[Table 2] The [4,4,0]Reverse turn mimetics library



No	R_2	R_4	R_7	R_1-Y'	Mol. Weight	M+H
1	2,4-Cl_2-benzyl	4-OH-benzyl	Allyl	OCH_3	533	534
2	2,4-Cl_2-benzyl	4-NO_2-benzyl	Allyl	OCH_3	562	563
3	2,4-Cl_2-benzyl	2,4-F_2-benzyl	Allyl	OCH_3	553	554
4	2,4-Cl_2-benzyl	4-Cl-benzyl	Allyl	OCH_3	552	553
5	2,4-Cl_2-benzyl	2,2-bisphenylethyl	Allyl	OCH_3	594	595
6	2,4-Cl_2-benzyl	3-t-Bu-4-OH-benzyl	Allyl	OCH_3	590	591
7	2,4-Cl_2-benzyl	4-Me-benzyl	Allyl	OCH_3	531	532
8	2,4-Cl_2-benzyl	Cyclohexyl-methyl	Allyl	OCH_3	523	524
9	2,4-Cl_2-benzyl	4-F-benzyl	Allyl	OCH_3	535	536
10	2,4-Cl_2-benzyl	2-Cl-benzyl	Allyl	OCH_3	552	553
11	2,4-Cl_2-benzyl	2,4-Cl_2-benzyl	Allyl	OCH_3	586	587
12	2,4-Cl_2-benzyl	Naphth-2-ylmethyl	Allyl	OCH_3	567	568
13	2,4-Cl_2-benzyl	4-OH-benzyl	Benzyl	OCH_3	583	584
14	2,4-Cl_2-benzyl	4-NO_2-benzyl	Benzyl	OCH_3	612	613
15	2,4-Cl_2-benzyl	2,4-F_2-benzyl	Benzyl	OCH_3	603	604
16	2,4-Cl_2-benzyl	4-Cl-benzyl	Benzyl	OCH_3	602	603

17	2,4-Cl_2-benzyl	2,2-bisphenylethyl	Benzyl	OCH_3	644	645
18	2,4-Cl_2-benzyl	3-t-Bu-4-OH-benzyl	Benzyl	OCH_3	640	641
19	2,4-Cl_2-benzyl	4-Me-benzyl	Benzyl	OCH_3	582	583
20	2,4-Cl_2-benzyl	Cyclohexyl-methyl	Benzyl	OCH_3	574	575
21	2,4-Cl_2-benzyl	4-F-benzyl	Benzyl	OCH_3	585	586
22	2,4-Cl_2-benzyl	2-Cl-benzyl	Benzyl	OCH_3	602	603
23	2,4-Cl_2-benzyl	2,4-Cl_2-benzyl	Benzyl	OCH_3	636	637
24	2,4-Cl_2-benzyl	Naphth-2-ylmethyl	Benzyl	OCH_3	618	619
25	2,4-Cl_2-benzyl	4-OH-benzyl	Allyl	OCH_3	479	480
26	2,4-Cl_2-benzyl	4-NO_2-benzyl	Allyl	OCH_3	508	509
27	2,4-Cl_2-benzyl	2,4-F_2-benzyl	Allyl	OCH_3	499	500
28	2,4-Cl_2-benzyl	4-Cl-benzyl	Allyl	OCH_3	497	498
29	Phenethyl	2,2-bisphenylethyl	Allyl	OCH_3	539	540
30	Phenethyl	3-t-Bu-4-OH-benzyl	Allyl	OCH_3	535	536
31	Phenethyl	4-Me-benzyl	Allyl	OCH_3	477	478
32	Phenethyl	Cyclohexyl-methyl	Allyl	OCH_3	469	470
33	Phenethyl	4-F-benzyl	Allyl	OCH_3	481	482
34	Phenethyl	2-Cl-benzyl	Allyl	OCH_3	497	498
35	Phenethyl	2,4-Cl_2-benzyl	Allyl	OCH_3	531	532
36	Phenethyl	Naphth-2-ylmethyl	Allyl	OCH_3	513	514
37	Phenethyl	4-OH-benzyl	Benzyl	OCH_3	529	530
38	Phenethyl	4-NO_2-benzyl	Benzyl	OCH_3	558	559
39	Phenethyl	2,4-F_2-benzyl	Benzyl	OCH_3	549	550
40	Phenethyl	4-Cl-benzyl	Benzyl	OCH_3	547	548
41	Phenethyl	2,2-bisphenylethyl	Benzyl	OCH_3	589	590
42	Phenethyl	3-t-Bu-4-OH-benzyl	Benzyl	OCH_3	585	586
43	Phenethyl	4-Me-benzyl	Benzyl	OCH_3	527	528
44	Phenethyl	Cyclohexyl-methyl	Benzyl	OCH_3	519	520
45	Phenethyl	4-F-benzyl	Benzyl	OCH_3	531	532
46	Phenethyl	2-Cl-benzyl	Benzyl	OCH_3	547	548
47	Phenethyl	2,4-Cl_2-benzyl	Benzyl	OCH_3	582	583
48	Phenethyl	Naphth-2-ylmethyl	Benzyl	OCH_3	563	564
49	Phenethyl	4-OH-benzyl	Allyl	OCH_3	497	498

50	Phenethyl	4-NO_2-benzyl	Allyl	OCH_3	526	527
51	Phenethyl	2,4-F_2-benzyl	Allyl	OCH_3	517	518
52	Phenethyl	4-Cl-benzyl	Allyl	OCH_3	515	516
53	4-F-phenylethyl	2,2-bisphenylethyl	Allyl	OCH_3	557	558
54	4-F-phenylethyl	3-t-Bu-4-OH-benzyl	Allyl	OCH_3	553	554
55	4-F-phenylethyl	4-Me-benzyl	Allyl	OCH_3	495	496
56	4-F-phenylethyl	Cyclohexyl-methyl	Allyl	OCH_3	487	488
57	4-F-phenylethyl	4-F-benzyl	Allyl	OCH_3	499	500
58	4-F-phenylethyl	2-Cl-benzyl	Allyl	OCH_3	515	516
59	4-F-phenylethyl	2,4-Cl_2-benzyl	Allyl	OCH_3	549	550
60	4-F-phenylethyl	Naphth-2-ylmethyl	Allyl	OCH_3	531	532
61	4-F-phenylethyl	4-OH-benzyl	Benzyl	OCH_3	547	548
62	4-F-phenylethyl	4-NO_2-benzyl	Benzyl	OCH_3	576	577
63	4-F-phenylethyl	2,4-F_2-benzyl	Benzyl	OCH_3	567	568
64	4-F-phenylethyl	4-Cl-benzyl	Benzyl	OCH_3	565	566
65	4-F-phenylethyl	2,2-bisphenylethyl	Benzyl	OCH_3	607	608
66	4-F-phenylethyl	3-t-Bu-4-OH-benzyl	Benzyl	OCH_3	603	604
67	4-F-phenylethyl	4-Me-benzyl	Benzyl	OCH_3	545	546
68	4-F-phenylethyl	Cyclohexyl-methyl	Benzyl	OCH_3	537	538
69	4-F-phenylethyl	4-F-benzyl	Benzyl	OCH_3	549	550
70	4-F-phenylethyl	2-Cl-benzyl	Benzyl	OCH_3	565	566
71	4-F-phenylethyl	2,4-Cl_2-benzyl	Benzyl	OCH_3	599	600
72	4-F-phenylethyl	Naphth-2-ylmethyl	Benzyl	OCH_3	581	582
73	4-F-phenylethyl	4-OH-benzyl	Allyl	OCH_3	509	510
74	4-F-phenylethyl	4-NO_2-benzyl	Allyl	OCH_3	538	539
75	4-F-phenylethyl	2,4-F_2-benzyl	Allyl	OCH_3	529	530
76	4-F-phenylethyl	4-Cl-benzyl	Allyl	OCH_3	527	528
77	4-MeO-phenylethyl	2,2-bisphenylethyl	Allyl	OCH_3	569	570
78	4-MeO-phenylethyl	3-t-Bu-4-OH-benzyl	Allyl	OCH_3	565	566
79	4-MeO-phenylethyl	4-Me-benzyl	Allyl	OCH_3	507	508
80	4-MeO-phenylethyl	Cyclohexyl-methyl	Allyl	OCH_3	499	500
81	4-MeO-phenylethyl	4-F-benzyl	Allyl	OCH_3	511	512

82	4-MeO-phenylethyl	2-Cl-benzyl	Allyl	OCH_3	527	528
83	4-MeO-phenylethyl	2,4-Cl_2-benzyl	Allyl	OCH_3	561	562
84	4-MeO-phenylethyl	Naphth-2-ylmethyl	Allyl	OCH_3	543	544
85	4-MeO-phenylethyl	4-OH-benzyl	Benzyl	OCH_3	559	560
86	4-MeO-phenylethyl	4-NO_2-benzyl	Benzyl	OCH_3	588	589
87	4-MeO-phenylethyl	2,4-F_2-benzyl	Benzyl	OCH_3	579	580
88	4-MeO-phenylethyl	4-Cl-benzyl	Benzyl	OCH_3	577	578
89	4-MeO-phenylethyl	2,2-bisphenylethyl	Benzyl	OCH_3	619	620
90	4-MeO-phenylethyl	3-t-Bu-4-OH-benzyl	Benzyl	OCH_3	615	616
91	4-MeO-phenylethyl	4-Me-benzyl	Benzyl	OCH_3	557	558
92	4-MeO-phenylethyl	Cyclohexyl-methyl	Benzyl	OCH_3	549	550
93	4-MeO-phenylethyl	4-F-benzyl	Benzyl	OCH_3	561	562
94	4-MeO-phenylethyl	2-Cl-benzyl	Benzyl	OCH_3	577	578
95	4-MeO-phenylethyl	2,4-Cl_2-benzyl	Benzyl	OCH_3	612	613
96	4-MeO-phenylethyl	Naphth-2-ylmethyl	Benzyl	OCH_3	593	594
97	Isoamyl	4-OH-benzyl	Styrylmethyl	OCH_3	521	522
98	Isoamyl	4-NO_2-benzyl	Styrylmethyl	OCH_3	550	551
99	Isoamyl	2,4-F_2-benzyl	Styrylmethyl	OCH_3	541	542
100	Isoamyl	4-Cl-benzyl	Styrylmethyl	OCH_3	539	540
101	Isoamyl	2,2-bisphenylethyl	Styrylmethyl	OCH_3	581	582
102	Isoamyl	3-t-Bu-4-OH-benzyl	Styrylmethyl	OCH_3	497	498
103	Isoamyl	4-Me-benzyl	Styrylmethyl	OCH_3	519	520
104	Isoamyl	Cyclohexyl-methyl	Styrylmethyl	OCH_3	511	512
105	Isoamyl	4-F-benzyl	Styrylmethyl	OCH_3	523	524
106	Isoamyl	2-Cl-benzyl	Styrylmethyl	OCH_3	539	540
107	Isoamyl	2,4-Cl_2-benzyl	Styrylmethyl	OCH_3	574	575
108	Isoamyl	Naphth-2-ylmethyl	Styrylmethyl	OCH_3	555	556

109	Isoamyl	4-OH-benzyl	2,6-Cl_2-benzyl	OCH_3	563	564
110	Isoamyl	4-NO_2-benzyl	2,6-Cl_2-benzyl	OCH_3	592	593
111	Isoamyl	2,4-F_2-benzyl	2,6-Cl_2-benzyl	OCH_3	583	584
112	Isoamyl	4-Cl-benzyl	2,6-Cl_2-benzyl	OCH_3	582	583
113	Isoamyl	2,2-bisphenylethyl	2,6-Cl_2-benzyl	OCH_3	624	625
114	Isoamyl	3-t-Bu-4-OH-benzyl	2,6-Cl_2-benzyl	OCH_3	540	541
115	Isoamyl	4-Me-benzyl	2,6-Cl_2-benzyl	OCH_3	562	563
116	Isoamyl	Cyclohexyl-methyl	2,6-Cl_2-benzyl	OCH_3	554	555
117	Isoamyl	4-F-benzyl	2,6-Cl_2-benzyl	OCH_3	565	566
118	Isoamyl	2-Cl-benzyl	2,6-Cl_2-benzyl	OCH_3	582	583
119	Isoamyl	2,4-Cl_2-benzyl	2,6-Cl_2-benzyl	OCH_3	616	617
120	Isoamyl	Naphth-2-ylmethyl	2,6-Cl_2-benzyl	OCH_3	598	599
121	3-MeO-propyl	4-OH-benzyl	Styrylmethyl	OCH_3	523	524
122	3-MeO-propyl	4-NO_2-benzyl	Styrylmethyl	OCH_3	552	553
123	3-MeO-propyl	2,4-F_2-benzyl	Styrylmethyl	OCH_3	543	544
124	3-MeO-propyl	4-Cl-benzyl	Styrylmethyl	OCH_3	541	542
125	3-MeO-propyl	2,2-bisphenylethyl	Styrylmethyl	OCH_3	583	584
126	3-MeO-propyl	3-t-Bu-4-OH-benzyl	Styrylmethyl	OCH_3	499	500
127	3-MeO-propyl	4-Me-benzyl	Styrylmethyl	OCH_3	521	522
128	3-MeO-propyl	Cyclohexyl-methyl	Styrylmethyl	OCH_3	513	514
129	3-MeO-propyl	4-F-benzyl	Styrylmethyl	OCH_3	525	526
130	3-MeO-propyl	2-Cl-benzyl	Styrylmethyl	OCH_3	541	542
131	3-MeO-propyl	2,4-Cl_2-benzyl	Styrylmethyl	OCH_3	575	576
132	3-MeO-propyl	Naphth-2-ylmethyl	Styrylmethyl	OCH_3	557	558
133	3-MeO-propyl	4-OH-benzyl	2,6-Cl_2-benzyl	OCH_3	565	566
134	3-MeO-propyl	4-NO_2-benzyl	2,6-Cl_2-benzyl	OCH_3	594	595
135	3-MeO-propyl	2,4-F_2-benzyl	2,6-Cl_2-benzyl	OCH_3	585	586

136	3-MeO-propyl	4-Cl-benzyl	2,6-Cl_2-benzyl	OCH_3	584	585
137	3-MeO-propyl	2,2-bisphenylethyl	2,6-Cl_2-benzyl	OCH_3	626	627
138	3-MeO-propyl	3-t-Bu-4-OH-benzyl	2,6-Cl_2-benzyl	OCH_3	541	542
139	3-MeO-propyl	4-Me-benzyl	2,6-Cl_2-benzyl	OCH_3	563	564
140	3-MeO-propyl	Cyclohexyl-methyl	2,6-Cl_2-benzyl	OCH_3	556	557
141	3-MeO-propyl	4-F-benzyl	2,6-Cl_2-benzyl	OCH_3	567	568
142	3-MeO-propyl	2-Cl-benzyl	2,6-Cl_2-benzyl	OCH_3	584	585
143	3-MeO-propyl	2,4-Cl_2-benzyl	2,6-Cl_2-benzyl	OCH_3	618	619
144	3-MeO-propyl	Naphth-2-ylmethyl	2,6-Cl_2-benzyl	OCH_3	600	601
145	4-MeO-phenylethyl	4-OH-benzyl	Styrylmethyl	OCH_3	585	586
146	4-MeO-phenylethyl	4-NO_2-benzyl	Styrylmethyl	OCH_3	614	615
147	4-MeO-phenylethyl	2,4-F_2-benzyl	Styrylmethyl	OCH_3	605	606
148	4-MeO-phenylethyl	4-Cl-benzyl	Styrylmethyl	OCH_3	603	604
149	4-MeO-phenylethyl	2,2-bisphenylethyl	Styrylmethyl	OCH_3	645	646
150	4-MeO-phenylethyl	3-t-Bu-4-OH-benzyl	Styrylmethyl	OCH_3	561	562
151	4-MeO-phenylethyl	4-Me-benzyl	Styrylmethyl	OCH_3	583	584
152	4-MeO-phenylethyl	Cyclohexyl-methyl	Styrylmethyl	OCH_3	575	576
153	4-MeO-phenylethyl	4-F-benzyl	Styrylmethyl	OCH_3	587	588
154	4-MeO-phenylethyl	2-Cl-benzyl	Styrylmethyl	OCH_3	603	604
155	4-MeO-phenylethyl	2,4-Cl_2-benzyl	Styrylmethyl	OCH_3	638	639
156	4-MeO-phenylethyl	Naphth-2-ylmethyl	Styrylmethyl	OCH_3	619	620
157	4-MeO-phenylethyl	4-OH-benzyl	2,6-Cl_2-benzyl	OCH_3	628	629
158	4-MeO-phenylethyl	4-NO_2-benzyl	2,6-Cl_2-benzyl	OCH_3	657	658

159	4-MeO-phenylethyl	2,4-F_2-benzyl	2,6-Cl_2-benzyl	OCH_3	648	649
160	4-MeO-phenylethyl	4-Cl-benzyl	2,6-Cl_2-benzyl	OCH_3	646	647
161	4-MeO-phenylethyl	2,2-bisphenylethyl	2,6-Cl_2-benzyl	OCH_3	688	689
162	4-MeO-phenylethyl	3-t-Bu-4-OH-benzyl	2,6-Cl_2-benzyl	OCH_3	604	605
163	4-MeO-phenylethyl	4-Me-benzyl	2,6-Cl_2-benzyl	OCH_3	626	627
164	4-MeO-phenylethyl	Cyclohexyl-methyl	2,6-Cl_2-benzyl	OCH_3	618	619
165	4-MeO-phenylethyl	4-F-benzyl	2,6-Cl_2-benzyl	OCH_3	630	631
166	4-MeO-phenylethyl	2-Cl-benzyl	2,6-Cl_2-benzyl	OCH_3	646	647
167	4-MeO-phenylethyl	2,4-Cl_2-benzyl	2,6-Cl_2-benzyl	OCH_3	680	681
168	4-MeO-phenylethyl	Naphth-2-ylmethyl	2,6-Cl_2-benzyl	OCH_3	662	663
169	Tetrahydrofuran-2-ylmethyl	4-OH-benzyl	Styrylmethyl	OCH_3	535	536
170	Tetrahydrofuran-2-ylmethyl	4-NO_2-benzyl	Styrylmethyl	OCH_3	564	565
171	Tetrahydrofuran-2-ylmethyl	2,4-F_2-benzyl	Styrylmethyl	OCH_3	555	556
172	Tetrahydrofuran-2-ylmethyl	4-Cl-benzyl	Styrylmethyl	OCH_3	553	554
173	Tetrahydrofuran-2-ylmethyl	2,2-bisphenylethyl	Styrylmethyl	OCH_3	595	596
174	Tetrahydrofuran-2-ylmethyl	3-t-Bu-4-OH-benzyl	Styrylmethyl	OCH_3	511	512
175	Tetrahydrofuran-2-ylmethyl	4-Me-benzyl	Styrylmethyl	OCH_3	533	534
176	Tetrahydrofuran-2-ylmethyl	Cyclohexyl-methyl	Styrylmethyl	OCH_3	525	526
177	Tetrahydrofuran-2-ylmethyl	4-F-benzyl	Styrylmethyl	OCH_3	537	538
178	Tetrahydrofuran-2-ylmethyl	2-Cl-benzyl	Styrylmethyl	OCH_3	553	554
179	Tetrahydrofuran-2-ylmethyl	2,4-Cl_2-benzyl	Styrylmethyl	OCH_3	588	589
180	Tetrahydrofuran-2-ylmethyl	Naphth-2-ylmethyl	Styrylmethyl	OCH_3	569	570
181	Tetrahydrofuran-2-ylmethyl	4-OH-benzyl	2,6-Cl_2-benzyl	OCH_3	577	578

182	Tetrahydrofuran -2-ylmethyl	4-NO_2-benzyl	2,6-Cl_2-benzyl	OCH_3	606	607
183	Tetrahydrofuran -2-ylmethyl	2,4-F_2-benzyl	2,6-Cl_2-benzyl	OCH_3	597	598
184	Tetrahydrofuran -2-ylmethyl	4-Cl-benzyl	2,6-Cl_2-benzyl	OCH_3	596	597
185	Tetrahydrofuran -2-ylmethyl	2,2-bisphenylethyl	2,6-Cl_2-benzyl	OCH_3	638	639
186	Tetrahydrofuran -2-ylmethyl	3-t-Bu-4-OH-benzyl	2,6-Cl_2-benzyl	OCH_3	553	554
187	Tetrahydrofuran -2-ylmethyl	4-Me-benzyl	2,6-Cl_2-benzyl	OCH_3	575	576
188	Tetrahydrofuran -2-ylmethyl	Cyclohexyl-methyl	2,6-Cl_2-benzyl	OCH_3	568	569
189	Tetrahydrofuran -2-ylmethyl	4-F-benzyl	2,6-Cl_2-benzyl	OCH_3	579	580
190	Tetrahydrofuran -2-ylmethyl	2-Cl-benzyl	2,6-Cl_2-benzyl	OCH_3	596	597
191	Tetrahydrofuran -2-ylmethyl	2,4-Cl_2-benzyl	2,6-Cl_2-benzyl	OCH_3	630	631
192	Tetrahydrofuran -2-ylmethyl	Naphth-2-ylmethyl	2,6-Cl_2-benzyl	OCH_3	612	613
193	Phenethyl	4-OH-benzyl	Methyl	(4-Me-phenyl)amino	528	529
194	Phenethyl	4-OH-benzyl	Methyl	(4-Cl-phenyl)amino	548	549
195	Phenethyl	4-OH-benzyl	Methyl	Phenylamino	514	515
196	Phenethyl	4-OH-benzyl	Methyl	((*R*)-α -methylbenzyl)amino	542	543
197	Phenethyl	4-OH-benzyl	Methyl	Benzylamino	528	529
198	Phenethyl	4-OH-benzyl	Methyl	(4-MeO-phenyl)amino	544	545
199	Phenethyl	4-OH-benzyl	Methyl	(4-Br-phenyl)amino	592	593
200	Phenethyl	4-OH-benzyl	Methyl	(4-CF_3-phenyl)amino	582	583
201	Phenethyl	4-OH-benzyl	Methyl	Pentylamino	508	509
202	Phenethyl	4-OH-benzyl	Methyl	(2-Phenylethyl)amino	542	543
203	Phenethyl	4-OH-benzyl	Methyl	(4-MeO-benzyl)amino	558	559
204	Phenethyl	4-OH-benzyl	Methyl	Cyclohexylamino	520	521
205	2,2-	4-OH-benzyl	Methyl	(4-Me-	604	605

	bisphenylethyl			phenyl)amino		
206	2,2-bisphenylethyl	4-OH-benzyl	Methyl	(4-Cl-phenyl)amino	624	625
207	2,2-bisphenylethyl	4-OH-benzyl	Methyl	Phenylamino	590	591
208	2,2-bisphenylethyl	4-OH-benzyl	Methyl	((*R*)-α-methylbenzyl)amino	618	619
209	2,2-bisphenylethyl	4-OH-benzyl	Methyl	Benzylamino	604	605
210	2,2-bisphenylethyl	4-OH-benzyl	Methyl	(4-MeO-phenyl)amino	620	621
211	2,2-bisphenylethyl	4-OH-benzyl	Methyl	(4-Br-phenyl)amino	669	670
212	2,2-bisphenylethyl	4-OH-benzyl	Methyl	(4-CF_3-phenyl)amino	658	659
213	2,2-bisphenylethyl	4-OH-benzyl	Methyl	Pentylamino	584	585
214	2,2-bisphenylethyl	4-OH-benzyl	Methyl	(2-Phenylethyl)amino	618	619
215	2,2-bisphenylethyl	4-OH-benzyl	Methyl	(4-MeO-benzyl)amino	634	635
216	2,2-bisphenylethyl	4-OH-benzyl	Methyl	Cyclohexylamino	596	597
217	Phenethyl	3,4-Cl_2-benzyl	Methyl	(4-Me-phenyl)amino	581	582
218	Phenethyl	3,4-Cl_2-benzyl	Methyl	(4-Cl-phenyl)amino	601	602
219	Phenethyl	3,4-Cl_2-benzyl	Methyl	Phenylamino	566	567
220	Phenethyl	3,4-Cl_2-benzyl	Methyl	((*R*)-α-methylbenzyl)amino	595	596
221	Phenethyl	3,4-Cl_2-benzyl	Methyl	Benzylamino	581	582
222	Phenethyl	3,4-Cl_2-benzyl	Methyl	(4-MeO-phenyl)amino	597	598
223	Phenethyl	3,4-Cl_2-benzyl	Methyl	(4-Br-phenyl)amino	645	646
224	Phenethyl	3,4-Cl_2-benzyl	Methyl	(4-CF_3-phenyl)amino	634	635
225	Phenethyl	3,4-Cl_2-benzyl	Methyl	Pentylamino	561	562
226	Phenethyl	3,4-Cl_2-benzyl	Methyl	(2-Phenylethyl)amino	595	596
227	Phenethyl	3,4-Cl_2-benzyl	Methyl	(4-MeO-benzyl)amino	611	612
228	Phenethyl	3,4-Cl_2-benzyl	Methyl	Cyclohexylami	573	574

				no		
229	2,2-bisphenylethyl	3,4-Cl_2-benzyl	Methyl	(4-Me-phenyl)amino	657	658
230	2,2-bisphenylethyl	3,4-Cl_2-benzyl	Methyl	(4-Cl-phenyl)amino	677	678
231	2,2-bisphenylethyl	3,4-Cl_2-benzyl	Methyl	Phenylamino	643	644
232	2,2-bisphenylethyl	3,4-Cl_2-benzyl	Methyl	((*R*)-α-methylbenzyl)amino	671	672
233	2,2-bisphenylethyl	3,4-Cl_2-benzyl	Methyl	Benzylamino	657	658
234	2,2-bisphenylethyl	3,4-Cl_2-benzyl	Methyl	(4-MeO-phenyl)amino	673	674
235	2,2-bisphenylethyl	3,4-Cl_2-benzyl	Methyl	(4-Br-phenyl)amino	721	722
236	2,2-bisphenylethyl	3,4-Cl_2-benzyl	Methyl	(4-CF_3-phenyl)amino	711	712
237	2,2-bisphenylethyl	3,4-Cl_2-benzyl	Methyl	Pentylamino	637	638
238	2,2-bisphenylethyl	3,4-Cl_2-benzyl	Methyl	(2-Phenylethyl)amino	671	672
239	2,2-bisphenylethyl	3,4-Cl_2-benzyl	Methyl	(4-MeO-benzyl)amino	687	688
240	2,2-bisphenylethyl	3,4-Cl_2-benzyl	Methyl	Cyclohexylamino	649	650
241	Isoamyl	4-OH-benzyl	Methyl	(4-Me-phenyl)amino	478	479
242	Isoamyl	4-OH-benzyl	Methyl	(4-Cl-phenyl)amino	498	499
243	Isoamyl	4-OH-benzyl	Methyl	Phenylamino	464	465
244	Isoamyl	4-OH-benzyl	Methyl	((*R*)-α-methylbenzyl)amino	492	493
245	Isoamyl	4-OH-benzyl	Methyl	Benzylamino	478	479
246	Isoamyl	4-OH-benzyl	Methyl	(4-MeO-phenyl)amino	494	495
247	Isoamyl	4-OH-benzyl	Methyl	(4-Br-phenyl)amino	542	543
248	Isoamyl	4-OH-benzyl	Methyl	(4-CF_3-phenyl)amino	532	533
249	Isoamyl	4-OH-benzyl	Methyl	Pentylamino	458	459
250	Isoamyl	4-OH-benzyl	Methyl	(2-Phenylethyl)amino	492	493
251	Isoamyl	4-OH-benzyl	Methyl	(4-MeO-	508	509

				benzyl)amino		
252	Isoamyl	4-OH-benzyl	Methyl	Cyclohexylamino	470	471
253	Isoamyl	4-OH-benzyl	Methyl	(4-Me-phenyl)amino	554	555
254	Isoamyl	4-OH-benzyl	Methyl	(4-Cl-phenyl)amino	574	575
255	Isoamyl	4-OH-benzyl	Methyl	Phenylamino	540	541
256	Isoamyl	4-OH-benzyl	Methyl	((*R*)-α - methylbenzyl)amino	568	569
257	Isoamyl	4-OH-benzyl	Methyl	Benzylamino	554	555
258	Isoamyl	4-OH-benzyl	Methyl	(4-MeO-phenyl)amino	570	571
259	Isoamyl	4-OH-benzyl	Methyl	(4-Br-phenyl)amino	619	620
260	Isoamyl	4-OH-benzyl	Methyl	(4-CF_3-phenyl)amino	608	609
261	Isoamyl	4-OH-benzyl	Methyl	Pentylamino	534	535
262	Isoamyl	4-OH-benzyl	Methyl	(2-Phenylethyl)amino	568	569
263	Isoamyl	4-OH-benzyl	Methyl	(4-MeO-benzyl)amino	584	585
264	Isoamyl	4-OH-benzyl	Methyl	Cyclohexylamino	546	547
265	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	(4-Me-phenyl)amino	526	527
266	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	(4-Cl-phenyl)amino	546	547
267	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	Phenylamino	512	513
268	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	((*R*)-α - methylbenzyl)amino	540	541
269	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	Benzylamino	526	527
270	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	(4-MeO-phenyl)amino	542	543
271	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	(4-Br-phenyl)amino	591	592
272	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	(4-CF_3-phenyl)amino	580	581
273	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	Pentylamino	506	507
274	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	(2-Phenylethyl)amino	540	541
275	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	(4-MeO-benzyl)amino	556	557

276	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	Cyclohexylamino	518	519
277	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	(4-Me-phenyl)amino	602	603
278	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	(4-Cl-phenyl)amino	622	623
279	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	Phenylamino	588	589
280	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	((*R*)-α-methylbenzyl)amino	616	617
281	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	Benzylamino	602	603
282	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	(4-MeO-phenyl)amino	618	619
283	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	(4-Br-phenyl)amino	667	668
284	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	(4-CF_3-phenyl)amino	656	657
285	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	Pentylamino	582	583
286	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	(2-Phenylethyl)amino	616	617
287	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	(4-MeO-benzyl)amino	632	633
288	4-methylbenzyl	3,4-Cl_2-benzyl	Methyl	Cyclohexylamino	594	595
289	Naphth-1-ylmethyl	4-OH-benzyl	Methyl	(N-Cbz-3-Indoleethyl)amino	751	752
290	Naphth-1-ylmethyl	4-OH-benzyl	Methyl	(Naphth-2-ylmethyl)amino	614	615
291	naphth-1-ylmethyl	4-OH-benzyl	Methyl	(2-Phenylethyl)amino	578	579
292	naphth-1-ylmethyl	4-OH-benzyl	Methyl	[2-(4-MeO-phenyl)ethyl]amino	608	609
293	naphth-1-ylmethyl	4-OH-benzyl	Methyl	(3-CF_3-benzyl)amino	632	633
294	naphth-1-ylmethyl	4-OH-benzyl	Methyl	(4-MeO-benzyl)amino	594	595
295	naphth-1-ylmethyl	4-OH-benzyl	Methyl	(4-F-phenylethyl)amino	596	597
296	naphth-1-	4-OH-benzyl	Methyl	(3,4-Cl_2-	633	634

	ylmethyl			benzyl)amino		
297	naphth-1-ylmethyl	4-OH-benzyl	Methyl	(2-HO-ethyl)amino	518	519
298	naphth-1-ylmethyl	4-OH-benzyl	Methyl	(3-MeO-propyl)amino	546	547
299	naphth-1-ylmethyl	4-OH-benzyl	Methyl	(Tetrahydrofuran-2-ylmethyl)amino	558	559
300	naphth-1-ylmethyl	4-OH-benzyl	Methyl	(cyclohexylmethyl)amino	570	571
301	naphth-1-ylmethyl	4-OH-benzyl	Propyl	(N-Cbz-3-Indoleethyl)amino	779	780
302	naphth-1-ylmethyl	4-OH-benzyl	Propyl	(Naphth-2-ylmethyl)amino	642	643
303	naphth-1-ylmethyl	4-OH-benzyl	Propyl	(2-Phenylethyl)amino	606	607
304	naphth-1-ylmethyl	4-OH-benzyl	Propyl	[2-(4-MeO-phenyl)ethyl]amino	636	637
305	naphth-1-ylmethyl	4-OH-benzyl	Propyl	(3-CF_3-benzyl)amino	660	661
306	naphth-1-ylmethyl	4-OH-benzyl	Propyl	(4-MeO-benzyl)amino	622	623
307	naphth-1-ylmethyl	4-OH-benzyl	Propyl	(4-F-phenylethyl)amino	624	625
308	naphth-1-ylmethyl	4-OH-benzyl	Propyl	(3,4-Cl_2-benzyl)amino	661	662
309	naphth-1-ylmethyl	4-OH-benzyl	Propyl	(2-HO-ethyl)amino	546	547
310	naphth-1-ylmethyl	4-OH-benzyl	Propyl	(3-MeO-propyl)amino	574	575
311	naphth-1-ylmethyl	4-OH-benzyl	Propyl	(Tetrahydrofuran-2-ylmethyl)amino	586	587
312	naphth-1-ylmethyl	4-OH-benzyl	Propyl	(cyclohexylmethyl)amino	598	599
313	naphth-1-ylmethyl	3,4-F_2-benzyl	Methyl	(N-Cbz-3-Indoleethyl)amino	771	772
314	naphth-1-	3,4-F_2-benzyl	Methyl	(Naphth-2-	634	635

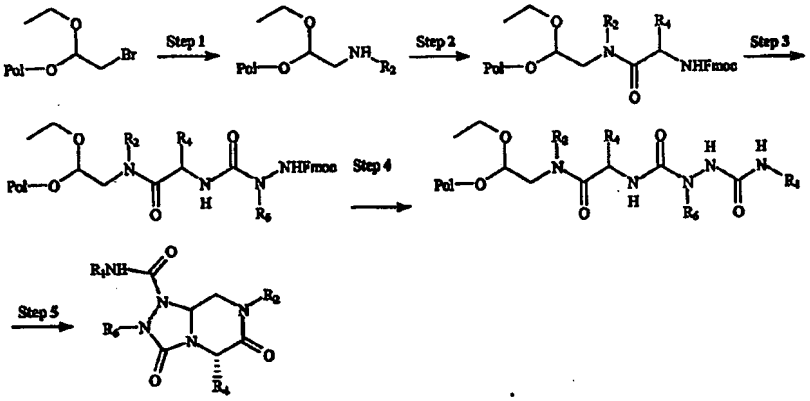
	ylmethyl			ylmethyl)amino		
315	naphth-1-ylmethyl	3,4-F_2-benzyl	Methyl	(2-Phenylethyl)amino	598	599
316	naphth-1-ylmethyl	3,4-F_2-benzyl	Methyl	[2-(4-MeO-phenyl)ethyl]amino	628	629
317	naphth-1-ylmethyl	3,4-F_2-benzyl	Methyl	(3-CF_3-benzyl)amino	652	653
318	naphth-1-ylmethyl	3,4-F_2-benzyl	Methyl	(4-MeO-benzyl)amino	614	615
319	Naphth-1-ylmethyl	3,4-F_2-benzyl	Methyl	(4-F-phenylethyl)amino	616	617
320	naphth-1-ylmethyl	3,4-F_2-benzyl	Methyl	(3,4-Cl_2-benzyl)amino	653	654
321	naphth-1-ylmethyl	3,4-F_2-benzyl	Methyl	(2-HO-ethyl)amino	538	539
322	naphth-1-ylmethyl	3,4-F_2-benzyl	Methyl	(3-MeO-propyl)mino	566	567
323	naphth-1-ylmethyl	3,4-F_2-benzyl	Methyl	(Tetrahydrofuran-2-ylmethyl)amino	578	579
324	Naphth-1-ylmethyl	3,4-F_2-benzyl	Methyl	(cyclohexylmethyl)amino	590	591
325	naphth-1-ylmethyl	3,4-F_2-benzyl	Propyl	(N-Cbz-3-Indoleethyl)amino	799	800
326	naphth-1-ylmethyl	3,4-F_2-benzyl	Propyl	(Naphth-2-ylmethyl)amino	662	663
327	Naphth-1-ylmethyl	3,4-F_2-benzyl	Propyl	(2-Phenylethyl)amino	626	627
328	Naphth-1-ylmethyl	3,4-F_2-benzyl	Propyl	[2-(4-MeO-phenyl)ethyl]amino	656	657
329	naphth-1-ylmethyl	3,4-F_2-benzyl	Propyl	(3-CF_3-benzyl)amino	680	681
330	Naphth-1-ylmethyl	3,4-F_2-benzyl	Propyl	(4-MeO-benzyl)amino	642	643
331	Naphth-1-ylmethyl	3,4-F_2-benzyl	Propyl	(4-F-phenylethyl)amino	644	645

332	Naphth-1-ylmethyl	3,4-F_2-benzyl	Propyl	(3,4-Cl_2-benzyl)amino	681	682
333	Naphth-1-ylmethyl	3,4-F_2-benzyl	Propyl	(2-HO-ethyl)amino	566	567
334	Naphth-1-ylmethyl	3,4-F_2-benzyl	Propyl	(3-MeO-propyl)mino	594	595
335	naphth-1-ylmethyl	3,4-F_2-benzyl	Propyl	(Tetrahydrofuran-2-ylmethyl)amino	606	607
336	Naphth-1-ylmethyl	3,4-F_2-benzyl	Propyl	(cyclohexylmethyl)amino	618	619
337	Naphth-1-ylmethyl	4-biphenylyl-methyl	Methyl	(N-Cbz-3-Indoleethyl)amino	811	812
338	Naphth-1-ylmethyl	4-biphenylyl-methyl	Methyl	(Naphth-2-ylmethyl)amino	674	675
339	Naphth-1-ylmethyl	4-biphenylyl-methyl	Methyl	(2-Phenylethyl)amino	638	639
340	Naphth-1-ylmethyl	4-biphenylyl-methyl	Methyl	[2-(4-MeO-phenyl)ethyl]amino	668	669
341	Naphth-1-ylmethyl	4-biphenylyl-methyl	Methyl	(3-CF_3-benzyl)amino	692	693
342	naphth-1-ylmethyl	4-biphenylyl-methyl	Methyl	(4-MeO-benzyl)amino	654	655
343	naphth-1-ylmethyl	4-biphenylyl-methyl	Methyl	(4-F-phenylethyl)amino	656	657
344	naphth-1-ylmethyl	4-biphenylyl-methyl	Methyl	(3,4-Cl_2-benzyl)amino	693	694
345	naphth-1-ylmethyl	4-biphenylyl-methyl	Methyl	(2-HO-ethyl)amino	578	579
346	Naphth-1-ylmethyl	4-biphenylyl-methyl	Methyl	(3-MeO-propyl)mino	606	607
347	Naphth-1-ylmethyl	4-biphenylyl-methyl	Methyl	(Tetrahydrofuran-2-ylmethyl)amino	618	619
348	Naphth-1-ylmethyl	4-biphenylyl-methyl	Methyl	(cyclohexylmethyl)amino	630	631
349	Naphth-1-ylmethyl	4-biphenylyl-methyl	Propyl	(N-Cbz-3-Indoleethyl)amino	839	840

350	Naphth-1-ylmethyl	4-biphenylyl-methyl	Propyl	(Naphth-2-ylmethyl)amino	702	703
351	Naphth-1-ylmethyl	4-biphenylyl-methyl	Propyl	(2-Phenylethyl)amino	666	667
352	naphth-1-ylmethyl	4-biphenylyl-methyl	Propyl	[2-(4-MeO-phenyl)ethyl]amino	696	697
353	naphth-1-ylmethyl	4-biphenylyl-methyl	Propyl	(3-CF_3-benzyl)amino	720	721
354	naphth-1-ylmethyl	4-biphenylyl-methyl	Propyl	(4-MeO-benzyl)amino	682	683
355	naphth-1-ylmethyl	4-biphenylyl-methyl	Propyl	(4-F-phenylethyl)amino	684	685
356	naphth-1-ylmethyl	4-biphenylyl-methyl	Propyl	(3,4-Cl_2-benzyl)amino	721	722
357	naphth-1-ylmethyl	4-biphenylyl-methyl	Propyl	(2-HO-ethyl)amino	606	607
358	Naphth-1-ylmethyl	4-biphenylyl-methyl	Propyl	(3-MeO-propyl)mino	634	635
359	Naphth-1-ylmethyl	4-biphenylyl-methyl	Propyl	(Tetrahydrofuran-2-ylmethyl)amino	646	647
360	Naphth-1-ylmethyl	4-biphenylyl-methyl	Propyl	(cyclohexylmethyl)amino	658	659
361	naphth-1-ylmethyl	3-t-Bu-4-OH-benzyl	Methyl	(N-Cbz-3-Indoleethyl)amino	807	808
362	Naphth-1-ylmethyl	3-t-Bu-4-OH-benzyl	Methyl	(Naphth-2-ylmethyl)amino	670	671
363	Naphth-1-ylmethyl	3-t-Bu-4-OH-benzyl	Methyl	(2-Phenylethyl)amino	634	635
364	Naphth-1-ylmethyl	3-t-Bu-4-OH-benzyl	Methyl	[2-(4-MeO-phenyl)ethyl]amino	664	665
365	naphth-1-ylmethyl	3-t-Bu-4-OH-benzyl	Methyl	(3-CF_3-benzyl)amino	688	689
366	naphth-1-ylmethyl	3-t-Bu-4-OH-benzyl	Methyl	(4-MeO-benzyl)amino	650	651
367	naphth-1-ylmethyl	3-t-Bu-4-OH-benzyl	Methyl	(4-F-phenylethyl)am	652	653

				ino		
368	naphth-1-ylmethyl	3-t-Bu-4-OH-benzyl	Methyl	(3,4-Cl_2-benzyl)amino	689	690
369	Naphth-1-ylmethyl	3-t-Bu-4-OH-benzyl	Methyl	(2-HO-ethyl)amino	574	575
370	naphth-1-ylmethyl	3-t-Bu-4-OH-benzyl	Methyl	(3-MeO-propyl)mino	602	603
371	naphth-1-ylmethyl	3-t-Bu-4-OH-benzyl	Methyl	(Tetrahydrofuran-2-ylmethyl)amino	614	615
372	naphth-1-ylmethyl	3-t-Bu-4-OH-benzyl	Methyl	(cyclohexylmethyl)amino	626	627
373	naphth-1-ylmethyl	3-t-Bu-4-OH-benzyl	Propyl	(N-Cbz-3-Indoleethyl)amino	835	836
374	naphth-1-ylmethyl	3-t-Bu-4-OH-benzyl	Propyl	(Naphth-2-ylmethyl)amino	698	699
375	Naphth-1-ylmethyl	3-t-Bu-4-OH-benzyl	Propyl	(2-Phenylethyl)amino	662	663
376	naphth-1-ylmethyl	3-t-Bu-4-OH-benzyl	Propyl	[2-(4-MeO-phenyl)ethyl]amino	692	693
377	naphth-1-ylmethyl	3-t-Bu-4-OH-benzyl	Propyl	(3-CF_3-benzyl)amino	716	717
378	naphth-1-ylmethyl	3-t-Bu-4-OH-benzyl	Propyl	(4-MeO-benzyl)amino	678	679
379	naphth-1-ylmethyl	3-t-Bu-4-OH-benzyl	Propyl	(4-F-phenylethyl)amino	680	681
380	naphth-1-ylmethyl	3-t-Bu-4-OH-benzyl	Propyl	(3,4-Cl_2-benzyl)amino	717	718
381	Naphth-1-ylmethyl	3-t-Bu-4-OH-benzyl	Propyl	(2-HO-ethyl)amino	602	603
382	naphth-1-ylmethyl	3-t-Bu-4-OH-benzyl	Propyl	(3-MeO-propyl)mino	630	631
383	naphth-1-ylmethyl	3-t-Bu-4-OH-benzyl	Propyl	(Tetrahydrofuran-2-ylmethyl)amino	642	643
384	naphth-1-ylmethyl	3-t-Bu-4-OH-benzyl	Propyl	(cyclohexylmethyl)amino	654	655

[0064] In addition, synthesis of the peptide mimetics of the library of the present invention may be accomplished using the General Scheme of [4,3,0] Reverse-Turn Mimetic Library as follows:



[0065] Synthesis of the peptide mimetics of the bicyclic template libraries of the present invention was accomplished using FlexChem Reactor Block which has 96 well plate by known techniques. In the above scheme 'Pol' represents Bromoacetal resin (Advanced ChemTech) and detailed procedure is illustrated bellow.

Step 1

[0066] The bromoacetal resin (1.6mmol/g) and a solution of R1 amine in DMSO(2M solution) were placed in 96 well Robbinns block (FlexChem). The reaction mixture was shaken at 60°C using rotating oven [robbins Scientific] for 12 hrs. The resin was washed with DMF, MeOH, then DCM.

Step 2

[0067] A solution of commercial available FmocAminoAcids (4eq.), PyBob (4eq), HOAt (4eq.), and DIEA (12 eq.) in DMF was added to the resin. After the

reaction mixture was shaken for 12 hrs at room temperature, the resin was washed with DMF, MeOH, and then DCM.

Step 3

[0068] To the resin swollen by DMF before reaction was added 25% piperidine in DMF. After the reaction mixture was shaken for 30 min at room temperature. This deprotection step was repeated again and then washed with DMF, Methanol, then DCM. A solution of hydrazine carbamoyl chloride (4 eq.), HOBt (4 eq.), and DIC (4 eq.) in DMF was added to the resin. After the reaction mixture was shaken for 12 hrs at room temperature, the resin was washed with DMF, MeOH, and then DCM.

Step 4

[0069] To the resin swollen by DMF before reaction was added 25% piperidine in DMF. After the reaction mixture was shaken for 30 min at room temperature. This deprotection step was repeated again and then washed with DMF, Methanol, then DCM. To the resin swollen by DCM before reaction was added R_1-isocynate (5 eq.) in DCM. After the reaction mixture was shaken for 12 hrs at room temperature the resin was washed with DMF, MeOH, then DCM.

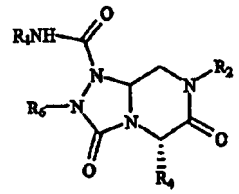
Step 5

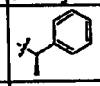
[0070] The resin was treated with formic acid (1.2 mL each well) for 18 hrs at room temperature. After the resin was removed by filtration, the filtrate was condensed under reduced pressure using SpeedVac [SAVANT] to give the product as oil. These products were diluted with 50% water/acetonitrile and then lyophilized after freezing.

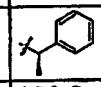
[0071] Table 3 shows a [4,3,0] Reverse turn mimetics library which can be prepared according to the present invention, of which representative preparation is given

in Example 5.

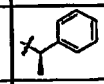
[Table 3]: The [4,3,0] Reverse turn mimetics library

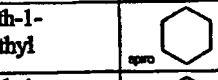
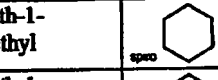
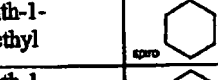
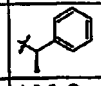
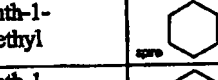
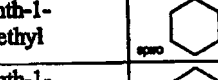
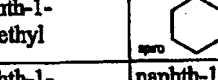


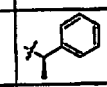
No	R_2	R_4	R_6	R_1	Mol. Weight	M+H
1	Isoamyl	4-OH-phenyl	Methyl	Phenyl	466	467
2	Isoamyl	4-OH-phenyl	methyl	4-Me-phenyl	480	481
3	Isoamyl	4-OH-phenyl	methyl	3,5-Me_2-phenyl	494	495
4	Isoamyl	4-OH-phenyl	methyl	4-MeO-phenyl	496	497
5	Isoamyl	4-OH-phenyl	methyl	4-CF_3-phenyl	534	535
6	Isoamyl	4-OH-phenyl	methyl	Cyclohexyl	472	473
7	Isoamyl	4-OH-phenyl	methyl	Benzyl	480	481
8	isoamyl	4-OH-phenyl	methyl		494	495
9	isoamyl	4-OH-phenyl	methyl	4-MeO-benzyl	510	511
10	isoamyl	4-OH-phenyl	methyl	Phenethyl	494	495
11	isoamyl	4-OH-phenyl	methyl	Pentyl	460	461
12	isoamyl	4-OH-phenyl	methyl	Hexyl	474	475
13	benzyl	4-OH-phenyl	methyl	Phenyl	486	487
14	benzyl	4-OH-phenyl	methyl	4-Me-phenyl	500	501
15	benzyl	4-OH-phenyl	methyl	3,5-Me_2-phenyl	514	515
16	benzyl	4-OH-phenyl	methyl	4-MeO-phenyl	516	517
17	benzyl	4-OH-phenyl	methyl	4-CF_3-phenyl	554	555
18	benzyl	4-OH-phenyl	methyl	Cyclohexyl	492	493
19	benzyl	4-OH-phenyl	methyl	Benzyl	500	501
20	benzyl	4-OH-phenyl	methyl		514	515
21	benzyl	4-OH-phenyl	methyl	4-MeO-benzyl	530	531
22	benzyl	4-OH-phenyl	methyl	Phenethyl	514	515

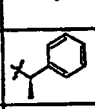
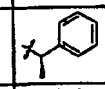
23	benzyl	4-OH-phenyl	methyl	Pentyl	480	481
24	benzyl	4-OH-phenyl	methyl	Hexyl	494	495
25	naphth-1-ylmethyl	4-OH-phenyl	methyl	Phenyl	536	537
26	naphth-1-ylmethyl	4-OH-phenyl	methyl	4-Me-phenyl	550	551
27	naphth-1-ylmethyl	4-OH-phenyl	methyl	3,5-Me_2-phenyl	564	565
28	naphth-1-ylmethyl	4-OH-phenyl	methyl	4-MeO-phenyl	566	567
29	naphth-1-ylmethyl	4-OH-phenyl	methyl	4-CF_3-phenyl	604	605
30	naphth-1-ylmethyl	4-OH-phenyl	methyl	Cyclohexyl	542	543
31	naphth-1-ylmethyl	4-OH-phenyl	methyl	Benzyl	550	551
32	naphth-1-ylmethyl	4-OH-phenyl	methyl		564	565
33	naphth-1-ylmethyl	4-OH-phenyl	methyl	4-MeO-benzyl	580	581
34	naphth-1-ylmethyl	4-OH-phenyl	methyl	Phenethyl	564	565
35	naphth-1-ylmethyl	4-OH-phenyl	methyl	Pentyl	530	531
36	naphth-1-ylmethyl	4-OH-phenyl	methyl	Hexyl	544	545
37	cyclohexylmethyl	4-OH-phenyl	methyl	Phenyl	492	493
38	cyclohexylmethyl	4-OH-phenyl	methyl	4-Me-phenyl	506	507
39	cyclohexylmethyl	4-OH-phenyl	methyl	3,5-Me_2-phenyl	520	521
40	cyclohexylmethyl	4-OH-phenyl	methyl	4-MeO-phenyl	522	523
41	cyclohexylmethyl	4-OH-phenyl	methyl	4-CF_3-phenyl	560	561
42	cyclohexylmethyl	4-OH-phenyl	methyl	Cyclohexyl	468	469
43	cyclohexylmethyl	4-OH-phenyl	methyl	Benzyl	506	507
44	cyclohexylmethyl	4-OH-phenyl	methyl		520	521
45	cyclohexylmethyl	4-OH-phenyl	methyl	4-MeO-benzyl	536	537
46	cyclohexylmethy	4-OH-phenyl	methyl	Phenethyl	520	521

	l					
47	cyclohexylmethyl	4-OH-phenyl	methyl	Pentyl	486	487
48	cyclohexylmethyl	4-OH-phenyl	methyl	Hexyl	500	501
49	4-methylbenzyl	4-OH-phenyl	methyl	Phenyl	500	501
50	4-methylbenzyl	4-OH-phenyl	methyl	4-Me-phenyl	514	515
51	4-methylbenzyl	4-OH-phenyl	methyl	3,5-Me_2-phenyl	528	529
52	4-methylbenzyl	4-OH-phenyl	methyl	4-MeO-phenyl	530	531
53	4-methylbenzyl	4-OH-phenyl	methyl	4-CF_3-phenyl	568	569
54	4-methylbenzyl	4-OH-phenyl	methyl	Cyclohexyl	506	507
55	4-methylbenzyl	4-OH-phenyl	methyl	Benzyl	514	515
56	4-methylbenzyl	4-OH-phenyl	methyl		528	529
57	4-methylbenzyl	4-OH-phenyl	methyl	4-MeO-benzyl	544	545
58	4-methylbenzyl	4-OH-phenyl	methyl	Phenethyl	528	529
59	4-methylbenzyl	4-OH-phenyl	methyl	Pentyl	494	495
60	4-methylbenzyl	4-OH-phenyl	methyl	Hexyl	508	509
61	methoxypropyl	4-OH-phenyl	methyl	Phenyl	468	469
62	methoxypropyl	4-OH-phenyl	methyl	4-Me-phenyl	482	483
63	methoxypropyl	4-OH-phenyl	methyl	3,5-Me_2-phenyl	496	497
64	methoxypropyl	4-OH-phenyl	methyl	4-MeO-phenyl	498	499
65	methoxypropyl	4-OH-phenyl	methyl	4-CF_3-phenyl	536	537
66	methoxypropyl	4-OH-phenyl	methyl	Cyclohexyl	474	475
67	methoxypropyl	4-OH-phenyl	methyl	Benzyl	482	483
68	methoxypropyl	4-OH-phenyl	methyl		496	497
69	methoxypropyl	4-OH-phenyl	methyl	4-MeO-benzyl	512	513
70	methoxypropyl	4-OH-phenyl	methyl	Phenethyl	496	497
71	methoxypropyl	4-OH-phenyl	methyl	Pentyl	462	463
72	methoxypropyl	4-OH-phenyl	methyl	Hexyl	476	477
73	phenethyl	4-OH-phenyl	methyl	Phenyl	500	501
74	phenethyl	4-OH-phenyl	methyl	4-Me-phenyl	514	515
75	phenethyl	4-OH-phenyl	methyl	3,5-Me_2-phenyl	528	529
76	phenethyl	4-OH-phenyl	methyl	4-MeO-phenyl	530	531
77	phenethyl	4-OH-phenyl	methyl	4-CF_3-phenyl	568	569

78	phenethyl	4-OH-phenyl	methyl	Cyclohexyl	506	507
79	phenethyl	4-OH-phenyl	methyl	Benzyl	514	515
80	phenethyl	4-OH-phenyl	methyl		528	529
81	phenethyl	4-OH-phenyl	methyl	4-MeO-benzyl	544	545
82	phenethyl	4-OH-phenyl	methyl	Phenethyl	528	529
83	phenethyl	4-OH-phenyl	methyl	Pentyl	494	495
84	phenethyl	4-OH-phenyl	methyl	Hexyl	508	509
85	2,2-bisphenylethyl	4-OH-phenyl	methyl	Phenyl	576	577
86	2,2-bisphenylethyl	4-OH-phenyl	methyl	4-Me-phenyl	590	591
87	2,2-bisphenylethyl	4-OH-phenyl	methyl	3,5-Me_2-phenyl	604	605
88	2,2-bisphenylethyl	4-OH-phenyl	methyl	4-MeO-phenyl	606	607
89	2,2-bisphenylethyl	4-OH-phenyl	methyl	4-CF_3-phenyl	644	645
90	2,2-bisphenylethyl	4-OH-phenyl	methyl	Cyclohexyl	582	583
91	2,2-bisphenylethyl	4-OH-phenyl	methyl	Benzyl	586	587
92	2,2-bisphenylethyl	4-OH-phenyl	methyl		604	605
93	2,2-bisphenylethyl	4-OH-phenyl	methyl	4-MeO-benzyl	620	621
94	2,2-bisphenylethyl	4-OH-phenyl	methyl	Phenethyl	604	605
95	2,2-bisphenylethyl	4-OH-phenyl	methyl	Pentyl	570	571
96	2,2-bisphenylethyl	4-OH-phenyl	methyl	Hexyl	584	585
97	naphth-1-ylmethyl	benzyl	methyl	Phenyl	520	521
98	naphth-1-ylmethyl	benzyl	methyl	4-Me-phenyl	534	535
99	naphth-1-ylmethyl	benzyl	methyl	3,5-Me_2-phenyl	548	549
100	naphth-1-ylmethyl	benzyl	methyl	4-MeO-phenyl	550	551
101	naphth-1-ylmethyl	benzyl	methyl	4-CF_3-phenyl	588	589
102	naphth-1-	benzyl	methyl	Cyclohexyl	526	527

	ylmethyl					
103	naphth-1-ylmethyl	benzyl	methyl	Benzyl	534	535
104	naphth-1-ylmethyl	benzyl	methyl		548	549
105	naphth-1-ylmethyl	benzyl	methyl	4-MeO-benzyl	564	565
106	naphth-1-ylmethyl	benzyl	methyl	Phenethyl	548	549
107	naphth-1-ylmethyl	benzyl	methyl	Pentyl	514	515
108	naphth-1-ylmethyl	benzyl	methyl	Hexyl	528	529
109	naphth-1-ylmethyl		methyl	Phenyl	498	499
110	naphth-1-ylmethyl		methyl	4-Me-phenyl	512	513
111	naphth-1-ylmethyl		methyl	3,5-Me_2-phenyl	526	527
112	naphth-1-ylmethyl		methyl	4-MeO-phenyl	528	529
113	naphth-1-ylmethyl		methyl	4-CF_3-phenyl	566	567
114	naphth-1-ylmethyl		methyl	Cyclohexyl	504	505
115	naphth-1-ylmethyl		methyl	Benzyl	512	513
116	naphth-1-ylmethyl		methyl		526	527
117	naphth-1-ylmethyl		methyl	4-MeO-benzyl	542	543
118	naphth-1-ylmethyl		methyl	Phenethyl	526	527
119	naphth-1-ylmethyl		methyl	Pentyl	492	493
120	naphth-1-ylmethyl		methyl	Hexyl	506	507
121	naphth-1-ylmethyl	naphth-1-ylmethyl	methyl	Phenyl	570	571

122	naphth-1-ylmethyl	naphth-1-ylmethyl	methyl	4-Me-phenyl	584	585
123	naphth-1-ylmethyl	naphth-1-ylmethyl	methyl	3,5-Me_2-phenyl	598	599
124	naphth-1-ylmethyl	naphth-1-ylmethyl	methyl	4-MeO-phenyl	600	601
125	naphth-1-ylmethyl	naphth-1-ylmethyl	methyl	4-CF_3-phenyl	638	639
126	naphth-1-ylmethyl	naphth-1-ylmethyl	methyl	Cyclohexyl	576	577
127	naphth-1-ylmethyl	naphth-1-ylmethyl	methyl	Benzyl	584	585
128	naphth-1-ylmethyl	naphth-1-ylmethyl	methyl		598	599
129	naphth-1-ylmethyl	naphth-1-ylmethyl	methyl	4-MeO-benzyl	614	615
130	naphth-1-ylmethyl	naphth-1-ylmethyl	methyl	Phenethyl	598	599
131	naphth-1-ylmethyl	naphth-1-ylmethyl	methyl	Pentyl	564	565
132	naphth-1-ylmethyl	naphth-1-ylmethyl	methyl	Hexyl	578	579
133	naphth-1-ylmethyl	cyclohexylmethyl	methyl	Phenyl	526	527
134	naphth-1-ylmethyl	cyclohexylmethyl	methyl	4-Me-phenyl	540	541
135	naphth-1-ylmethyl	cyclohexylmethyl	methyl	3,5-Me_2-phenyl	554	555
136	naphth-1-ylmethyl	cyclohexylmethyl	methyl	4-MeO-phenyl	556	557
137	naphth-1-ylmethyl	cyclohexylmethyl	methyl	4-CF_3-phenyl	594	595
138	naphth-1-ylmethyl	cyclohexylmethyl	methyl	Cyclohexyl	532	533
139	naphth-1-ylmethyl	cyclohexylmethyl	methyl	Benzyl	540	541
140	naphth-1-ylmethyl	cyclohexylmethyl	methyl		554	555
141	naphth-1-ylmethyl	cyclohexylmethyl	methyl	4-MeO-benzyl	570	571
142	naphth-1-ylmethyl	cyclohexylmethyl	methyl	Phenethyl	554	555
143	naphth-1-ylmethyl	cyclohexylmethyl	methyl	Pentyl	520	521

144	naphth-1-ylmethyl	cyclohexylmethyl	methyl	Hexyl	534	535
145	naphth-1-ylmethyl	4-chlorobenzyl	methyl	Phenyl	554	555
146	naphth-1-ylmethyl	4-chlorobenzyl	methyl	4-Me-phenyl	568	569
147	naphth-1-ylmethyl	4-chlorobenzyl	methyl	3,5-Me_2-phenyl	582	583
148	naphth-1-ylmethyl	4-chlorobenzyl	methyl	4-MeO-phenyl	584	585
149	naphth-1-ylmethyl	4-chlorobenzyl	methyl	4-CF_3-phenyl	622	623
150	naphth-1-ylmethyl	4-chlorobenzyl	methyl	Cyclohexyl	560	561
151	naphth-1-ylmethyl	4-chlorobenzyl	methyl	Benzyl	568	569
152	naphth-1-ylmethyl	4-chlorobenzyl	methyl		582	583
153	naphth-1-ylmethyl	4-chlorobenzyl	methyl	4-MeO-benzyl	598	599
154	naphth-1-ylmethyl	4-chlorobenzyl	methyl	Phenethyl	582	583
155	naphth-1-ylmethyl	4-chlorobenzyl	methyl	Pentyl	548	549
156	naphth-1-ylmethyl	4-chlorobenzyl	methyl	Hexyl	562	563
157	naphth-1-ylmethyl	methyl	methyl	Phenyl	444	445
158	naphth-1-ylmethyl	methyl	methyl	4-Me-phenyl	458	459
159	naphth-1-ylmethyl	methyl	methyl	3,5-Me_2-phenyl	472	473
160	naphth-1-ylmethyl	methyl	methyl	4-MeO-phenyl	474	475
161	naphth-1-ylmethyl	methyl	methyl	4-CF_3-phenyl	512	513
162	naphth-1-ylmethyl	methyl	methyl	Cyclohexyl	450	451
163	naphth-1-ylmethyl	methyl	methyl	Benzyl	458	459
164	naphth-1-ylmethyl	methyl	methyl		472	473
165	naphth-1-ylmethyl	methyl	methyl	4-MeO-benzyl	488	489

166	naphth-1-ylmethyl	methyl	methyl	Phenethyl	472	473
167	naphth-1-ylmethyl	methyl	methyl	Pentyl	438	439
168	naphth-1-ylmethyl	methyl	methyl	Hexyl	452	453
169	naphth-1-ylmethyl	isobutyl	methyl	Phenyl	486	487
170	naphth-1-ylmethyl	isobutyl	methyl	4-Me-phenyl	500	501
171	naphth-1-ylmethyl	isobutyl	methyl	3,5-Me_2-phenyl	514	515
172	naphth-1-ylmethyl	isobutyl	methyl	4-MeO-phenyl	516	517
173	naphth-1-ylmethyl	isobutyl	methyl	4-CF_3-phenyl	554	555
174	naphth-1-ylmethyl	isobutyl	methyl	Cyclohexyl	492	493
175	naphth-1-ylmethyl	isobutyl	methyl	Benzyl	500	501
176	naphth-1-ylmethyl	isobutyl	methyl		514	515
177	naphth-1-ylmethyl	isobutyl	methyl	4-MeO-benzyl	530	531
178	naphth-1-ylmethyl	isobutyl	methyl	Phenethyl	514	515
179	naphth-1-ylmethyl	isobutyl	methyl	Pentyl	480	481
180	naphth-1-ylmethyl	isobutyl	methyl	Hexyl	494	495
181	naphth-1-ylmethyl	methylthioethyl	methyl	Phenyl	504	505
182	naphth-1-ylmethyl	Methylthioethyl	methyl	4-Me-phenyl	518	519
183	naphth-1-ylmethyl	Methylthioethyl	methyl	3,5-Me_2-phenyl	532	533
184	naphth-1-ylmethyl	Methylthioethyl	methyl	4-MeO-phenyl	534	535
185	naphth-1-ylmethyl	Methylthioethyl	methyl	4-CF_3-phenyl	572	573
186	naphth-1-ylmethyl	Methylthioethyl	methyl	Cyclohexyl	510	511
187	naphth-1-ylmethyl	Methylthioethyl	methyl	Benzyl	518	519

188	naphth-1-ylmethyl	Methylthioethyl	methyl		532	533
189	naphth-1-ylmethyl	Methylthioethyl	methyl	4-MeO-benzyl	548	549
190	Naphth-1-ylmethyl	Methylthioethyl	methyl	Phenethyl	532	533
191	Naphth-1-ylmethyl	Methylthioethyl	methyl	Pentyl	498	499
192	Naphth-1-ylmethyl	Methylthioethyl	methyl	Hexyl	512	513

[0072] In a further aspect of this invention, methods for screening the libraries for bioactivity and isolating bioactive library members are disclosed. The libraries of the present invention may be screened for bioactivity by a variety of techniques and methods. Generally, the screening assay may be performed by (1) contacting a library with a biological target of interest, such as a receptor, and allowing binding to occur between the mimetics of the library and the target, and (2) detecting the binding event by an appropriate assay, such as by the calorimetric assay disclosed by Lam et al. (*Nature* 354:82-84, 1991) or Griminski et al. (*Biotechnology* 12:1008-1011, 1994) (both of which are incorporated herein by reference). In a preferred embodiment, the library members are in solution and the target is immobilized on a solid phase. Alternatively, the library may be immobilized on a solid phase and may be probed by contacting it with the target in solution.

[0073] It is found in the present invention that the compound of general formula (I), especially the compound of general formula (VI) can inhibit CBP-mediated transcriptional activation in cancer cells by specifically binding to CBP, and it is supported by immunoprecipitation of CBP of SW480 cells with the compound of the present invention. Compound of the present invention also inhibits survivin expression in SW480 cells, and therefore inhibits oncogenic activity in cancer cells.

Thus, the compound of the present invention can be used for inhibiting cancer cells, and thus would be useful for the regulation of cell growth. Supporting such results, compound of the present invention further shows that it can induce caspase-3 activation in SW480 cells, and therefore inducing the apoptotic activity in cells. Thus, the compound of the present invention can be also advantageously used for inducing apoptosis in cells.

[0074] In another aspect of the present invention, a pharmaceutical composition containing the compound having the general formula (I), especially the compound of general formula (VI) is disclosed. For the preparation of the pharmaceutical composition containing the present compounds, a skilled person in the art can use publicly known knowledge and techniques which are known in the pertinent art. Generally known varieties of carriers and other additives are used for the preparation of the composition of the present invention. The composition containing the compound of general formula (I), especially the compound of general formula (VI) can be used for treatment of disorders modulated by Wnt signaling pathway, especially cancer, more especially colorectal cancer.

[0075] In another aspect of the present invention, a method for inhibiting the growth of tumor cell in a subject in which the method comprises administering to a tumor cell a safe and effective amount of the compounds of the present invention is disclosed. The composition containing such compounds also can be used for the inhibition of tumor cells. Thus, this method can be useful to treat cancer in a mammalian subject. It can be advantageously used for treating colorectal cancer.

[0076] In another aspect of the present invention, a method for treating a disorder modulated by Wnt signaling pathway in which the method comprises

administering to a patient a safe and effective amount of the compounds having general formula (I), especially the compound of general formula (VI) is disclosed. Pharmaceutical composition containing the compound of the present invention can be also used for this purpose. In this connection, it is found in the present invention that the compounds having general formula (I), especially the compound of general formula (VI) or the pharmaceutical composition containing thereof can be useful for the treatment of disorder modulated by TCF4 - β catenin – CBP complex, which is believed to be responsible for initiating the overexpression of cancer cells related to Wnt signaling pathway. Thus, it is another aspect of the present invention to provide a method for the treatment of disorder modulated by TCF4 - β catenin – CBP complex, using the compounds having the general formula (I), especially the compound of general formula (VI).

[0077] Further, because the treatment of cancer is also closely related to inducing apoptosis in cancer cells in a subject, the present invention is also directed to a method of inducing apoptosis in cancer cells using the compounds of general formula (I), especially the compound of general formula (VI).

[0078] It has been known from previous art that 5-FU [Fluorouracil; 5-fluoro-2,4(1H, 3H)-pyrimidinedione] can induce apoptosis in cultured oral cancer cells (D. Tong et al., Oral Oncology 36, 2000 236-241). Further, it is also known that colon cancer has a sensitivity to 5-FU (D. Arango et al., Cancer Research 61, 2001 4910-4915). In the present invention, therefore, the combination of 5-FU having established anti-cancer activity and the compounds of formula (I), especially the compound of general formula (VI) of the present invention is prepared and tested against SW480 cell lines. As a result, it is found that the combination of 5-FU with the compounds of the

present invention, especially TCF4 compound, has a remarkable effect for inhibiting cancer cell growth such as SW480 cells.

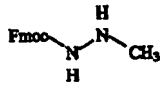
[0079] Therefore, it is yet another aspect of the present invention to provide a method of treating cancer, which comprises administering to a subject a safe and effective amounts of the compound having formula (I) of Claim 1, especially the compound of general formula (VI), together with other anti-cancer agent such as 5-Fu.

[0080] The following non-limiting examples illustrate the compound, composition, and methods of use of this invention.

EXAMPLES

Preparation Example 1 : Preparation of (*N*-Fmoc-*N'*-R_3-hydrazino)-acetic acid

(1) Preparation of *N*-Fmoc-*N'*-Methyl Hydrazine



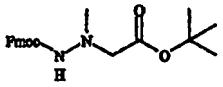
[0081] 2 L, two-neck, round-bottomed-flask was fitted with a glass stopper and a calcium tube. A solution of methylhydrazine sulfate(20 g, 139 mmol) in THF(300 mL) was added and a solution of DiBoc(33 g, 153 mmol) in THF was added. Sat. Sodium bicarbonate aqueous solution(500mL) was added dropwise via addition funnel over 2 hrs with vigorous stirring. After 6 hr, A solution of Fmoc-Cl (39 g, 153 mmol) in THF was added slowly. Resulting suspension was stirred for 6 hrs at 0°C. The mixture was extracted with EA(500 mL) and the organic layer was retained. The solution was dried with sodium sulfate and evaporated *in vacuo*. The next step was proceeded without purification.

[0082] 1 L, two-necked, round-bottom-flask was fitted with a glass stopper and

a calcium tube. A solution of reaction mixture in MeOH(300mL) was added and a conc. HCl(30 mL, 12 N) was added slowly via addition funnel with magnetic stirring in ice water bath and stirred overnight. The mixture was extracted with EA (1000 mL) and the organic layer was retained. The solution was dried with sodium sulfate and evaporated *in vacuo*. The residue was purified crystallization with n-hexane and EA to give product(32.2 g, 83 %).

[0083] 1HNMR(DMSO-D6) δ 7.90~7.88(d, *J*=6 Hz, 2H,), δ 7.73~7.70(d, *J*=9 Hz, 2H,), 7.44~7.31(m, 4H), 4.52~4.50(d, *J*=6 Hz, 2H), 4.31~4.26(t, *J*=6 Hz, 1H), 2.69(s, 1H)

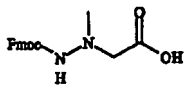
(2) Preparation of (*N*-Fmoc-*N'*-methyl-hydrazino)-acetic acid t-butyl ester



[0084] 1 L, two-necked, round-bottom-flask was fitted with a glass stopper and reflux condenser connected to a calcium tube. A solution of *N*-Fmoc-*N'*-Methyl-Hydrazine (20 g, 75 mmol) in toluene(300 mL) was added. A solution of t-butylbromo acetate (22 g, 111 mmol) in toluene(50mL) was added slowly. Cs_2CO_3 (49 g, 149 mmol) was added slowly. NaI (11 g, 74 mmol) was added slowly with vigorous stirring. The reaction mixture was stirred at reflux temperature over 1 day. A mixture was filtered and extracted the organic layer with ethyl acetate[EA] (500 mL). The solution was dried with sodium sulfate and evaporated *in vacuo*. The product was purified by chromatography with hexane : EA = 2 : 1 solution to give product(19.8 g, 70 %).

[0085] ^{1}HNMR($CDCl_3$-d) δ 7.78~7.75(d, *J*=9 Hz, 2H,), δ 7.61~7.59(d, *J*=6 Hz, 2H,), 7.43~7.26(m, 4H), 4.42~4.40(d, *J*=6 Hz, 2H), 4.23 (b, 1H), 3.57 (s, 2H), 2.78(s, 3H), 1.50(s, 9H)

(3) Preparation of (*N*-Fmoc-*N'*-methyl-hydrazino)-acetic acid

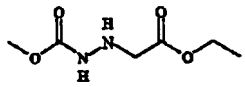


[0086] 1 L, two-neck, round-bottomed-flask was fitted with a glass stopper and reflux condenser connected to a calcium tube. (*N*-Fmoc-*N'*-methyl-hydrazino)-acetic acid t-butyl ester (20 g, 52 mmol) was added. A solution of HCl (150 mL, 4 M solution in dioxane) was added slowly with vigorous stirring in an ice water bath. The reaction mixture was stirred at RT over 1 day. The solution was concentrated completely under reduced pressure at 40 °C. The saturated aq. $NaHCO_3$ solution(100 mL) was added and the aqueous layer was washed with diethyl ether(100 mL). The conc. HCl was dropwised slowly at 0 °C(pH 2-3). The mixture was extracted and the organic layer was retained (500 mL, MC). The solution was dried with sodium sulfate and evaporated *in vacuo*. The residue was purified by recrystallization with n-hexane and ethyl acetate to give product(12 g, 72 %).

[0087] ^{1}HNMR(DMSO-d6) δ 12.38(s, 1H), 8.56(b, 1H), 7.89~7.86(d, *J*=9 Hz, 2H,), δ 7.70~7.67(d, *J*=9 Hz, 2H,), 7.43~7.29(m, 4H), 4.29~4.27(d, *J*=6 Hz, 2H), 4.25~4.20 (t, *J*=6 Hz, 1H), 3.47 (s, 2H), 2.56(s, 3H)

Preparation Example 2 : Preparation of (*N*-Moc-*N'*-R$_7$-hydrazino)-acetic acid

(1) Preparation of (*N'*-Methoxycarbonyl-hydrazino)-acetic acid ethyl ester

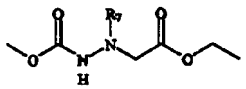


[0088] The methyl carbazate(50g, 0.55mol) was dissolved in DMF(300ml), and then ethyl bromoacetate(68ml, 0.555mol), potassium carbonate(77g, 0.555mol) were added to the reaction vessel. The mixture was warmed to 50°C for 5hrs. After the

reaction was completed, the mixture was filtered, and diluted with EtOAc, and washed with brine(3 times). The crude product was purified by column(eluent : Hex/EtOAc = 4/1).

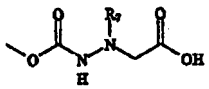
Pdt : 72g (colorless oil)

(2) [*N*-R_7-*N'*-methoxycarbonyl-hydrazino]-acetic acid ethyl ester



[0089] The ethyl ester(10g, 0.05 mol) , potassium carbonate(6.9g, 0.05mol), and R_3-bromide(14.1g, 0.06mol) were dissolved in DMF(200ml), and The mixture was warmed to 50°C for 5hrs. After the reaction was completed, the mixture was filtered, and diluted with EA, and washed with brine(3 times). The crude product was purified by Chromatography.(eluent : Hex/EtOAc = 4/1).

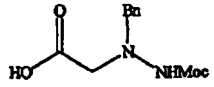
(3) [*N*-R_7-*N'*-methoxycarbonyl-hydrazino]-acetic acid



[0090] The alkylated ethyl ester(9.5g, 0.03mol) was dissolved in THF/water(1/1, ml), and added 2N NaOH(28.3ml) solution at 0°c. The mixture was stirred at RT for 2h. After the starting ester was not detected on UV, the solution was diluted with EA, then separated. The aqueous layer was acidified to pH 3~4 by 1N HCl, and the compound was extracted by DCM(3 times). The combined organic layer was dried over MgSO4, and evaporated to give a yellow solid.

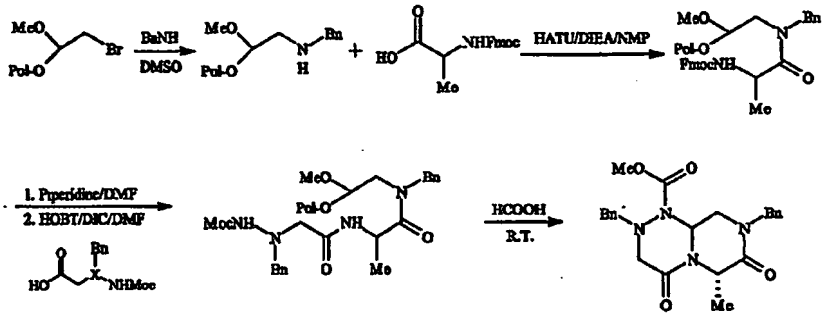
EXAMPLE 1

(1) Preparation of N^{β}-Moc-N^{α}-benzyl-hydrazinoglycine



[0091] This compound was prepared according to literature procedure. (Chegrillaume et. al., *Synlett* 2000, 3, 331)

(2) Preparation of 1-Methoxycarbonyl-2,8-dibenzyl-6-methyl-4,7-dioxo-hexahydro-pyrazino[2,1-c][1,2,4]triazine



[0092] The bromoacetal resin (60 mg, 0.98 mmol/g) and a solution of benzyl amine in DMSO (2.5 ml, 2 M) were placed in vial with screw cap. The reaction mixture was shaken at 60 °C using rotating oven [Robbins Scientific] for 12 h. The resin was collected by filtration, and washed with DMF, then DCM.

[0093] A solution of Fmoc-alanine (4 equiv.), HATU [PerSeptive Biosystems] (4 equiv.), and DIEA (4 equiv.) in NMP (Advanced ChemTech) was added to the resin. After the reaction mixture was shaken for 4 hrs at room temperature, the resin was collected by filtration and washed with DMF, DCM, and then DMF.

[0094] To the resin was added 20% piperidine in DMF. After the reaction mixture was shaken for 8 min at room temperature, the resin was collected by filtration and washed with DMF, DCM, and then DMF.

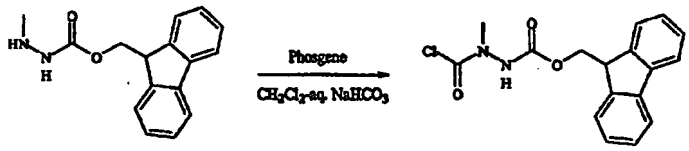
[0095] A solution of N^{α}-Moc-N^{α}-benzyl-hydrazinoglycine (4 equiv.), HOBT [Advanced ChemTech] (4 equiv.), and DIC (4 equiv.) in DMF was added to the resin prepared above. After the reaction mixture was shaken for 3 hrs at room temperature, the resin was collected by filtration and washed with DMF, DCM, and then MeOH. The resin was dried *in vacuo* at room temperature

[0096] The resin was treated with formic acid (2.5 ml) for 18 hrs at room temperature. After the resin was removed by filtration, the filtrate was condensed under reduced pressure to give the product as an oil.

[0097] ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm; 1.51 (d, 3H), 2.99 (m, 1H), 3.39 (d, 1H), 3.69 (m, 1H), 3.75 (m, 1H), 3.82 (s, 3H), 4.02(d, 1H), 4.24 (d, 1H), 4.39 (d, 1H), 4.75 (d, 1H), 5.14 (q, 1H), 5.58 (dd, 1H), 7.10-7.38 (m, 10H).

EXAMPLE 2

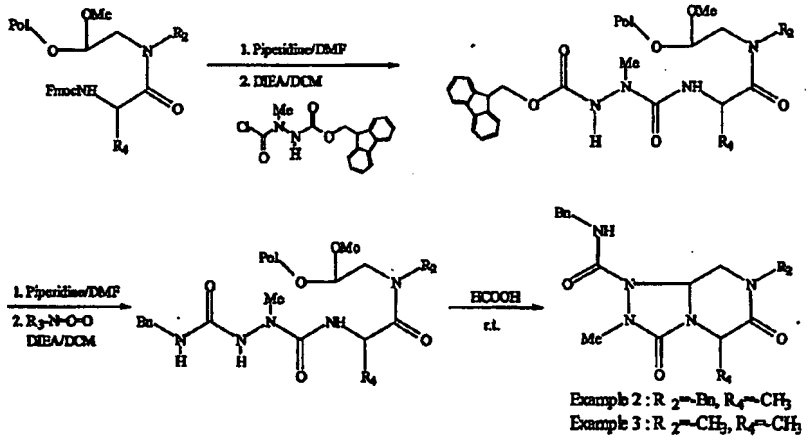
(1) Preparation of N^{α}-Fmoc-*N*-methyl-hydrazinocarbonyl chloride



[0098] An ice-cooled biphasic mixture of N-Methyl hydrazine carboxylic acid 9H-Fluoren-9-ylmethyl ester (107 mg, 0.4 mmol) in 15 ml of CH_2Cl_2 and 15 ml of saturated aq. $NaHCO_3$ was rapidly stirred while a 1.93 M phosgene in toluene (1.03 ml, 2 mmol) was added as a single portion. The reaction mixture was stirred for 30 min, the

organic phase was collected, and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford 128 mg (97 %) of carbamoyl chloride as a foamy solid. [Caution: Phosgene vapor is highly toxic-use hood] This product was used for the following solid phase synthesis without further purification.

(2) Preparation of 2,5-Dimethyl-7-benzyl-3,6-dioxo-hexahydro-[1,2,4]triazolo[4,5-a]pyrazine-1-carboxylic acid benzylamide



[0099] The bromoacetal resin (30 mg, 0.98 mmol/g) and a solution of benzyl amine in DMSO (1.5 ml, 2 M) were placed in vial with screw cap. The reaction mixture was shaken at 60 °C using rotating oven [Robbins Scientific] for 12 h. The resin was collected by filtration, and washed with DMF, then DCM.

[0100] A solution of Fmoc-alanine (3 equiv.), HATU [PerSeptive Biosystems] (3 equiv.), and DIEA (3 equiv.) in NMP (Advanced ChemTech) was added to the resin.

After the reaction mixture was shaken for 4 hrs at room temperature, the resin was collected by filtration and washed with DMF, DCM, and then DMF.

[0101] To the resin was added 20% piperidine in DMF. After the reaction mixture was shaken for 8 min at room temperature, the resin was collected by filtration and washed with DMF, DCM, and then DMF.

[0102] A solution of *N'*-Fmoc-*N*-methyl-hydrazinocarbonyl chloride (5 equiv.) obtained in the above step (1), DIEA (5 equiv.) in DCM was added to the resin prepared above. After the reaction mixture was shaken for 4 hrs at room temperature, the resin was collected by filtration and washed with DMF, DCM, and DMF.

[0103] To the resin was added 20% piperidine in DMF (10 ml for 1 g of the resin). After the reaction mixture was shaken for 8 min at room temperature, the resin was collected by filtration and washed with DMF, DCM, and then DMF.

[0104] The resin was treated with a mixture of benzyl isocyanate (4 equiv.) and DIEA (4 equiv.) in DCM for 4 hrs at room temperature. Then, the resin was collected by filtration and washed with DMF, DCM, and then MeOH. The resin was dried *in vacuo* at room temperature.

[0105] The resin was treated with formic acid for 14 hrs at room temperature. After the resin was removed by filtration, the filtrate was condensed under reduced pressure to give the product as an oil.

[0106] ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm; 1.48 (d, 3H), 2.98 (s, 3H), 3.18 (m, 1H), 3.46 (m, 1H), 4.37-4.74 (m, 5H), 5.66 (dd, 1H), 6.18 (m, 1H), 7.10-7.40 (m, 10H).

[0107] **EXAMPLE 3**

Preparation of 2,5,7-Trimethyl-3,6-dioxo-hexahydro-[1,2,4]triazolo[4,5-a]pyrazine-1-carboxylic acid benzylamide

[0108] The title compound is prepared according to the same procedure with Example 2.

[0109] ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm; 1.48 (d, 3H), 2.99 (s, 3H), 3.03(s, 3H), 3.38 (m, 1H), 3.53 (dd, 1H), 4.36 (dd, 1H), 4.52 (q, 1H), 4.59 (dd, 1H), 5.72 (dd, 1H), 6.19 (br.t, 1H), 7.10-7.38 (m, 5H).

[0110] **EXAMPLE 4**

Preparation of 2-Methyl-5-(*p*-hydroxyphenylmethyl)-7-naphthylmethyl-3,6-dioxo-hexahydro-[1,2,4]triazolo[4,5-a]pyrazine-1-carboxylic acid benzylamide

[0111] The bromoacetal resin (30 mg, 0.98 mmol/g) and a solution of naphthylmethyl amine in DMSO (1.5 ml, 2 M) were placed in vial with screw cap. The

reaction mixture was shaken at 60 °C using rotating oven [Robbins Scientific] for 12 h. The resin was collected by filtration, and washed with DMF, then DCM.

[0112] A solution of Fmoc-Tyr(OBut)-OH (3 eq.), HATU [PerSeptive Biosystems] (3 eq.), and DIEA (3 eq.) in NMP (Advanced ChemTech) was added to the resin. After the reaction mixture was shaken for 4 hrs at room temperature, the resin was collected by filtration and washed with DMF, DCM, and then DMF.

[0113] To the resin was added 20% piperidine in DMF. After the reaction mixture was shaken for 8 min at room temperature, the resin was collected by filtration and washed with DMF, DCM, and then DMF.

[0114] A solution of *N'*-Fmoc-*N*-methyl-hydrazinocarbonyl chloride (5 eq.), DIEA (5 eq.) in DCM was added to the resin prepared above. After the reaction mixture was shaken for 4 hrs at room temperature, the resin was collected by filtration and washed with DMF, DCM, and DMF.

[0115] To the resin was added 20% piperidine in DMF (10 ml for 1 g of the resin). After the reaction mixture was shaken for 8 min at room temperature, the resin was collected by filtration and washed with DMF, DCM, and then DMF.

[0116] The resin was treated with a mixture of benzyl isocyanate (4 eq.) and DIEA (4 eq.) in DCM for 4 hrs at room temperature. Then, the resin was collected by

filtration and washed with DMF, DCM, and then MeOH. The resin was dried *in vacuo* at room temperature.

[0117] The resin was treated with formic acid for 14 hrs at room temperature. After the resin was removed by filtration, the filtrate was condensed under reduced pressure to give the product as an oil.

[0118] ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm; 2.80-2.98 (m, 5H), 3.21-3.37 (m, 2H), 4.22-4.52 (m, 2H), 4.59 (t, 1H), 4.71 (d, 1H), 5.02 (dd, 1H), 5.35 (d, 1H), 5.51 (d, 1H), 6.66 (t, 2H), 6.94 (dd, 2H), 7.21-8.21 (m, 12H).

[0119] **EXAMPLE 5**

Preparation of 2-Methyl-6-(*p*-hydroxyphenylmethyl)-8-naphthyl-4,7-dioxo-hexahydro-pyrazino[2,1-c][1,2,4]triazine-1-carboxylic acid benzylamide

[0120] The bromoacetal resin (60 mg, 0.98 mmol/g) and a solution of naphthyl amine in DMSO (2.5 ml, 2 M) were placed in vial with screw cap. The reaction mixture was shaken at 60 °C using rotating oven [Robbins Scientific] for 12 h. The resin was collected by filtration, and washed with DMF, then DCM.

[0121] A solution of Fmoc- Tyr(OBut)-OH (4 eq.), HATU [PerSeptive Biosystems] (4 eq.), and DIEA (4 eq.) in NMP (Advanced ChemTech) was added to the

resin. After the reaction mixture was shaken for 4 hrs at room temperature, the resin was collected by filtration and washed with DMF, DCM, and then DMF.

[0122] To the resin was added 20% piperidine in DMF. After the reaction mixture was shaken for 8 min at room temperature, the resin was collected by filtration and washed with DMF, DCM, and then DMF.

[0123] A solution of N^{β}-Moc-N^{α}-benzyl-hydrazinoglycine (4 eq.), HOBT [Advanced ChemTech] (4 eq.), and DIC (4 eq.) in DMF was added to the resin prepared above. After the reaction mixture was shaken for 3 hrs at room temperature, the resin was collected by filtration and washed with DMF, and then DCM. To the resin was added 20% piperidine in DMF (10 ml for 1 g of the resin). After the reaction mixture was shaken for 8 min at room temperature, the resin was collected by filtration and washed with DMF, DCM, and then DMF.

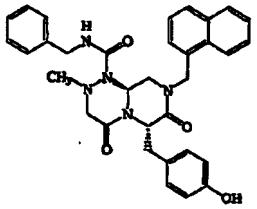
[0124] The resin was treated with a mixture of benzyl isocyanate (4 eq.) and DIEA (4 eq.) in DCM for 4 hrs at room temperature. Then, the resin was collected by filtration and washed with DMF, DCM, and then MeOH. After the resin was dried *in vacuo* at room temperature, the resin was treated with formic acid (2.5 ml) for 18 hrs at room temperature. The resin was removed by filtration, and the filtrate was condensed under reduced pressure to give the product as an oil.

[0125] ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm; 2.73 (s, 3H), 3.13 (d, 1H), 3.21-3.38 (m, 3H), 3.55 (d, 1H), 3.75 (t, 1H), 4.22 (dd, 1H), 4.36 (dd, 1H), 4.79 (d, 1H), 5.22 (t, 1H), 5.47 (m, 2H), 6.68 (d, 2H), 6.99 (d, 2H), 7.21-8.21 (m, 12H);

MS (m/z, ESI) 564.1 (MH^+) 586.3 (MNa^+).

[0126] **EXAMPLE 6**

Bioassay for the measurement of IC_{50} against SW480 cells of the following compound (Test compound has been prepared in the Example 4.):



[0127] SW480 cells were transfected with the usage of Superfect™ transfect reagent (Qiagen, 301307). Cells were trypsinized briefly 1 day before transfection and plated on 6 well plate (5×10^5 cells/well) so that they were 50-80% confluent on the day of transfection. Four microgram (TOPFlash) and one microgram (pRL-null) of DNAs were diluted in 150 µl of serum-free medium, and 30 µl of Superfect™ transfect reagent was added. The DNA-Superfect mixture was incubated at room temperature for 15 min, after that 1 ml of 10 % FBS DMEM was added to this complex for an additional 3 hrs of incubation. While complexes were forming, cells were washed with

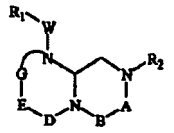
PBS twice without antibiotics. The DNA- Superfect™ transfect reagent complexes were applied to the cells before incubating at 37 °C at 5 % CO_2 for 3 h. After incubation, recovery medium with 10 % FBS was added to bring the final volume to 1.18 ml. After 3 hrs incubation, the cells were harvested and reseeded to 96 well plate (3×10^4 cells/well). After overnight incubation at 37 °C at 5 % CO_2, the test compounds were treated for 24 hrs. Finally, the activity was checked with luciferase assay (Promega, E1960).

[0128] Fig. 1 illustrates the results of the measurement of IC50 of the above compound for SW480 cells.

[0129] It will be appreciated that, although specific embodiments of the invention have been described herein for the purposes of illustration, various modifications may be made without departing from the spirit and scope of the invention. Accordingly, the invention is not limited except by the appended claims.

We claim:

1. A compound having the following general formula (I):



(I)

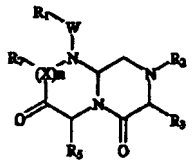
wherein A is -(CHR$_3$)- or -(C=O)-, B is -(CHR$_4$)- or -(C=O)-, D is –(CHR$_5$)- or –(C=O)-, E is –(ZR$_6$)- or -(C=O)-, G is –(XR$_7$)$_n$-, -(CHR$_7$)-(NR$_8$)-, -(C=O)-(XR$_9$)-, or -(C=O)- , W is –Y(C=O)-, -(C=O)NH-, -(SO$_2$)- or nothing, Y is oxygen or sulfur, X and Z are independently nitrogen or CH, n=0 or 1; and R$_1$, R$_2$, R$_3$, R$_4$, R$_5$, R$_6$, R$_7$, R$_8$ and R$_9$ are the same or different and independently selected from an amino acid side chain moiety or derivative thereof, the remainder of the molecule, a linker and a solid support, and stereoisomers thereof.

2. The compound of claim 1, wherein R$_1$, R$_2$, R$_3$, R$_4$, R$_5$, R$_6$, R$_7$, R$_8$ and R$_9$ are independently selected from the group consisting of aminoC$_{2-5}$alkyl, guamidinoC$_{2-5}$alkyl, C$_{1-4}$alkylguanidinoC$_{2-5}$alkyl, diC$_{1-4}$alkylguanidino-C$_{2-5}$alkyl, amidinoC$_{2-5}$alkyl,C$_{1-4}$alkylamidinoC$_{2-5}$alkyl, diC$_{1-4}$alkylamidinoC$_{2-5}$alkyl, C$_{1-3}$alkoxy, Phenyl, substituted phenyl(where the substituents are independently selected from one or more of amino, amidino, guanidine, hydrazine, amidrazonyl, C$_{1-4}$alkylamino, C$_{1-4}$dialkylamino, halogen, perfluoro C$_{1-4}$alkyl, C$_{1-4}$alkyl, C$_{1-3}$alkoxy, nitro, carboxy, cyano, sulfuryl, or hydroxyl), benzyl, substituted benzyl (where the substituents on the benzyl are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C$_{1-4}$alkylamino, C$_{1-4}$dialkylamino, halogen, perfluoro C$_{1-4}$alkyl, C$_{1-3}$alkoxy, nitro, carboxy,

cyano, sulfuryl, or hydroxyl), naphthyl, substituted naphthyl(where the substituents are independently selected from one or more of amino, amidino, guanidine, hydrazine, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl, or hydroxyl), bis-phenyl methyl, substituted bis-phenyl methyl(where the substituents are independently selected from one or more of amino, amidino, guanidine, hydrazine, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl, or hydroxyl), pyridyl, substituted pyridyl, (where the substituents are independently selected from one or more of amino amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl, or hydroxyl), pyridylC_{1-4}alkyl, substituted pyridylC_{1-4}alkyl (where the pyridine substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl, or hydroxyl), pyrimidylC_{1-4}alkyl, substituted pyrimidylC_{1-4}alkyl (where the pyrimidine substituents are independently selected from one or more of amino, amidino, guanidine, hydrazine, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy or nitro, carboxy, cyano, sulfuryl, or hydroxyl), triazin-2-yl-C_{1-4}alkyl, substituted triazin-2-yl-C_{1-4}alkyl (where the triazine substituents are independently selected from one or more of amino, amidino, guanidine, hydrazine, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl, or hydroxyl), imidazoC_{1-4}alkyl, substituted imidazol C_{1-4}alkl (where the imidazole sustituents are independently selected from one or more of amino, amidino, guanidine, hydrazine, amidrazonyl, C_{1-4}alkylamino, C_{1-}

$_4$dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl, or hydroxyl), imidazolinylC_{1-4}alkyl, N-amidinopiperazinyl-N-C_{0-4}alkyl, hydroxyC_{2-5}alkyl, C_{1-5}alkylaminoC_{2-5}alkyl, hydroxyC_{2-5}alkyl, C_{1-5}alkylaminoC_{2-5}alkyl, C_{1-5}dialkylaminoC_{2-6}alkyl, N-amidinopiperidinylC_{1-4}alkyl and 4-aminocyclohexylC_{0-2}alkyl;

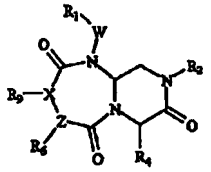
3. The compound of claim 1 wherein A is $-(CHR_3)-$, B is $-(C=O)-$, D is $-(CHR_5)-$, E is $-(C=O)-$, G is $-(XR_7)_n-$, and the compound has the following general formula (II):



(II)

wherein R_1, R_2, R_3, R_5, R_7, W, X and n are as defined in claim 1.

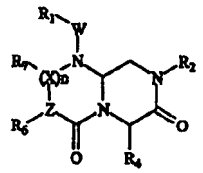
4. The compound of claim 1 wherein A is $-(C=O)-$, B is $-(CHR_4)-$, D is $-(C=O)-$, E is $-(ZR_6)-$, G is $-(C=O)-(XR_9)-$, and the compound has the following general formula (III):



(III)

wherein R_1, R_2, R_4, R_6, R_9, W and X are as defined in claim 1, Z is nitrogen or CH (when Z is CH, then X is nitrogen).

5. The compound of claim 1 wherein A is –(C=O)-, B is –(CHR_4)-, D is –(C=O)-, E is –(ZR_6)-, G is (XR_7)$_n$-, and the compound has the following general formula (IV):



(IV)

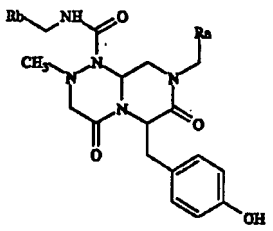
wherein R_1, R_2, R_4, R_6, R_7, W, X and n are as defined in claim 1, and Z is nitrogen or CH (when Z is nitrogen, then n is zero, and when Z is CH, then X is nitrogen and n is not zero).

6. The compound of claim 2 wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8 or R_9 is joined to a solid support or solid support derivatives.

7. The compound of claim 3 wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8 or R_9 is joined to a solid support or solid support derivatives.

8. The compound of claim 4 wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8 or R_9 is joined to a solid support or solid support derivatives.

9. The compound of claim 5, wherein the compound has the following general formula (VI):



(VI)

wherein, R_a is a bicyclic aryl group having 8 to 11 ring members, which may have 1 to 3 heteroatoms selected from nitrogen, oxygen or sulfur, and R_b is a monocyclic aryl group having 5 to 7 ring members, which may have 1 to 2 heteroatoms selected from nitrogen, oxygen or sulfur, and aryl ring in the compound may have one or more substituents selected from a group consisting of halide, hydroxy, cyano, lower alkyl, and lower alkoxy group.

10. The compound of claim 9, wherein R_a is naphthyl, quinolinyl or isoquinolinyl group, and R_b is phenyl, pyridyl or piperidyl, all of which may be substituted with one or more substituents selected from a group consisting of halide, hydroxy, cyano, lower alkyl, and lower alkoxy group.

11. The compound of claim 9, wherein R_a is naphthyl, and R_b is phenyl, which may be substituted with one or more substituents selected from a group consisting of halide, hydroxy, cyano, lower alkyl, and lower alkoxy group.

12. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

13. A pharmaceutical composition comprising a compound of claim 9 and a pharmaceutically acceptable carrier.

14. A method for inhibiting the growth of tumor cell in a mammalian subject, the method comprising administering to a tumor cell a safe and effective amount of the compound of claim 1.

15. A method for inhibiting the growth of tumor cell in a mammalian subject, the method comprising administering to a tumor cell a safe and effective amount of the compound of claim 9.

16. A method according to Claim 14 in which the tumor cell is colorectal cells.

17. A method according to Claim 15 in which the tumor cell is colorectal cells.

18. A method of treating cancer comprising administering to a subject safe and effective amounts of the compound of Claim 1 and of 5-FU.

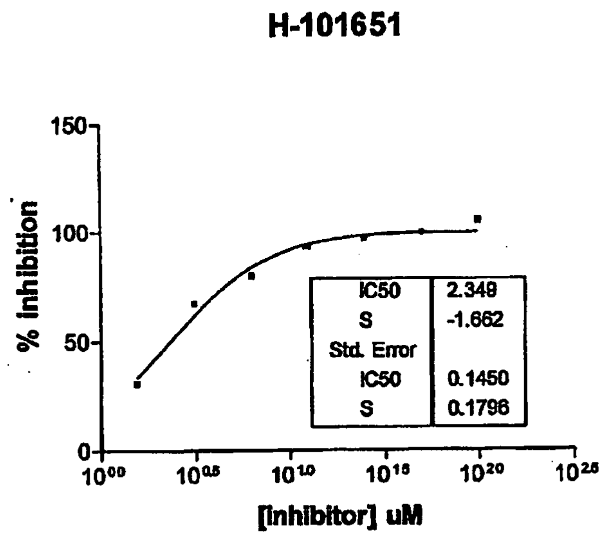
19. A library of compounds, comprising at least one compound of claim 1.

20. A method of identifying a biologically active compound, comprising contacting the library of claim 19 with a target to detect or screen the biologically active compound.

ABSTRACT

[0130] Conformationally constrained compounds which mimic the secondary structure of reverse-turn regions of biologically active peptides and proteins are disclosed. Such reverse-turn mimetic structures have utility over a wide range of fields, including use as diagnostic and therapeutic agents. Libraries containing the reverse-turn mimetic structures of this invention are also disclosed as well as methods for screening the same to identify biologically active members. The invention also relates to the use of such compounds for inhibiting or treating disorders modulated by Wnt-signaling pathway, such as cancer, especially colorectal cancer.

Figure 1/1


H-101651
150
100
50
0
% Inhibition
IC50 2.349
S -1.662
Std. Error
IC50 0.1450
S 0.1796
$10^{0.0}$
$10^{0.5}$
$10^{1.0}$
$10^{1.5}$
$10^{2.0}$
$10^{2.5}$
[Inhibitor] uM

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P-1306-PC1	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IL00/00496	International filing date *(day/month/year)* 16 August 2000 (16.08.2000)	Priority date *(day/month/year)* 16 August 1999 (16.08.1999)
International Patent Classification (IPC) or national classification and IPC IPC(7): G06F 17/60, 15/16, 17/30, 9/445; H04L 9/32 and US Cl.: 705/26, 40, 44, 53, 56; 709/238		
Applicant TRIVNET, LTD.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of ___ sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19 March 2001	12 December 2002 (12.12.2002)
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Heather Herndon Peggy Harod Telephone No. 703.305.3900

Form PCT/IPEA/409 (cover sheet)(July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/IL00/00496

I. Basis of the report

1. With regard to the elements of the international application:*

☒ the international application as originally filed.

☒ the description:
pages 1-43 as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the claims:
pages 44-60, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the drawings:
pages 1-13, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☐ the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages NONE

☐ the claims, Nos. NONE

☐ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/IL00/00496

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims	35-38,40-41,43-46,48-54	YES
	Claims	1-34,39,42,47	NO
Inventive Step (IS)	Claims	44-45	YES
	Claims	1-43,46-54	NO
Industrial Applicability (IA)	Claims	1-54	YES
	Claims	NONE	NO

2. CITATIONS AND EXPLANATIONS
Please See Continuation Sheet

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Claims 1-34 and 46 lack novelty under PCT article 33(2) as being anticipated by WILF et al., WO 99/08218 A1, published 18 February1999.

Per independent claims 1-34 and 46, WILF et al. identically discloses and claims all claimed steps. Claims 1-35 of the '218 WILF et al. patent are identical to claims 1-35 of the present claims, and claim 43 of the '218 patent/ publication is identical to claim 43 of the present application. Therefore, the claims had been fully disclosed by the Wilf et al. '218 before Applicant's priority date. Since the claims are identical, i.e., as a one-to-one correspondence, it is unnecessary to "copy/ paste" the entire contents of the claims identically disclosed in the present opinion.

Claims 1-2, 5, and 52-53 lack novelty under PCT article 33(2) as being anticipated by EGENDORF , WO 97/03410 A1, published 30 January 1997.

Per independent claim 1, EGENDORF discloses a method of performing a commercial transaction, wherein a customer uses a customer computer station (4.1-FIG. 1)that is connected to a network (3) to establish a connection with a vendor application (6.1) that runs on a server that is connected to the network, the method comprising the steps of (all of FIG. 1);

establishing a connection from the customer computer station to the vendor application via a network services provider (step 12, FIG. 2; "Internet access providers"-page 3, line 15) ;

initiating a transaction with the vendor application (step 13-FIG. 2);

receiving, by the network service provider, customer identity information from the. customer computer station (step 23-FIG. 3);

transferring customer transaction information to a transaction service ("provider can obtain approval from a third party to bill... the billing account"-page 16, lines 1-2);

providing transaction authorization to the vendor application (Provider 2 can then send verifying information to one or both the customer and the vendor"-page 14, lines 17-20); and

providing a product associated with the transaction ("shipment of goods"-page 10, line 7).

Per dependent claim 2, EIGENDORF further discloses :

extracting, by the transaction service, the customer identity information from the network service provider ("identifying information relating to the customer"-page 14, lines 2-4) and

wherein the method further includes the step of associating, by the transaction service, the customer ,identity, information with a financial account ("bill the transaction amount to the billing account"-col. 6, lines 1-3).

Per dependent claim 5, EGENDORF further discloses:

extracting, by the transaction service, customer identity information associated with an IP address from the network service provider ("Provider can extract the information from the exchange of information taking place between the customer and the vendor through the equipment of provider"-page 14, lines 11-17; "may include identifying information relating to the customer, such as the customers Internet address"-page 14, lines 2-4); and

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

associating, by the transaction service, the customer identity information with a financial account ("bill the transaction to the billing account"-page 16, lines 1-3).

Per dependent claim 52; EGENDORF demonstrates claimed "tangible good" (element 15--FIG. 4).

Per dependent claim 53; EGENDORF further discloses claimed obtaining an address (element 14--FIG. 2).

Claims 10-19, 42 lack novelty under PCT article 33(2) as being anticipated by MELEN et al. WO 97/29584 A1, published 14 August 1997.

Per independent claim 10, MELEN et al. demonstrates a method of performing a commercial transaction, wherein a customer uses d customer's computer station that is connected to, a network (11)t o establish a connection with a vendor application (S1... S2), that runs on a server that is connected to the network (12), the method comprising g the steps of (all of FIG. 1):

establishing a connection from the customer computer station to
the vendor application viva network service provider ("the user moves to a service advertised on the WWW-page"-page 7, lines 2-7);

initiating a transaction with the vendor application ("makes a purchase"-page 7, line 9);

establishing a connection from the customer computer station to a transaction server ("Both the device location C' and the given Internet address I are informed to the intelligent network"-page 6, lines 18-23; see entirety of page 6, lines 12 to line 24),

obtaining identity information for the customer (page 4, line 31 to page 5 line 2)

determining whether the customer is authorized to conduct the transaction (" the exchange 4 identifies whether the A subscriber's number is included in the number space having access to the B numbers"-page 9, lines 4-14); .

providing transaction authorization to the vendor application ("In other cases the access is prevented or blocked"-page 6, line 3; A's subscriber's access to the MAN net ... is restricted"-page 12, lines 21-26; "If the user is allowed access in the MAN-net, the PROXY server 8 send information about this through the signaling network"-page 11, lines 14-18);

providing a product associated with the transaction; and recording details related the transaction (page 7, lines 13-23)..

Per dependent claim 11; MELEN et al. further discloses: obtaining step includes the step of extracting, by the transaction server, the identity information from the network service provider ("PROXY server sends information about this through the signaling network to the intelligent network ... for use by the billing program"-page 4, line 31 to page 5, line 2). and wherein the determining step includes the step of associating, by the transaction server, the identity Information with a financial account (*idem.*--page 4, line 31 to page 5, line 2).

Per dependent claim 12; MELEN et al. comprises caller ID information (SCP has record of the users A number"-page 10, lines 10-11).

Per dependent claim 13; MELEN et al. discloses obtaining step comprises the steps of extracting, by the transaction server, identity information associated With an IP address from the network service provider; and associating, by the transaction server, the identity info information with a financial account (page 11, line 32 to page 12, line 7).

Per dependent claim 14, MELEN et al. obtains the true IP address (page 9, lines 30-36) in the event of a PROXY 8 (FIG. 1).

Per independent claim 15; MELEN et al. discloses:

establishing a plurality of vendor accounts with the "network service provide (*inherent* S1, S2...-FIG. 2; "The server can transmit the information about the purchase to the intelligent network 14 SCP for use by the billing program... "agreement with the tele-operator"-page 5, lines 19-21))r: -

commencing a transaction between one of the customers and one of the vendors via the network service provider ("chargeable service... obtainable from the certain IP address-page 7, lines 1-11):

obtaining identity information for the one customer (page 7, lines 5-11);

determining whether one of the customer accounts ("telephone bill"-page 4, lines 31-33), Is associated with the one customer providing transaction authorization to the one vendor (page 7, line 13-24);

debiting a customer account that is associated with the one customer (page 7, lines 13-22), and

crediting a vendor account that is associated with the one vendor (agreement with the tele-operator"-page 5, lines 19-21)

Per dependent claim 16; MELEN et al. discloses extracting claimed data from the service provider (page 7, lines 1-11)

Per dependent claim 17, MELEN et al. discloses caller id information (page 7, lines 4-9).

Per dependent claim 18, MELEN et al. obtains information from the network provider regarding limitation (page 7, lines 1-11; page 1, lines 32-34).

Per dependent claim 19, MELEN et al. discloses obtaining users IP information in the case of a proxy 8-FIG. 2.

Claim 39 lacks novelty under PCT article 33(2) as being anticipated by NIEMINEN et al, EP 924,630 A1, published 23 June 1999.

Per independent claim 39, NIEMINEN et al. discloses a method for filtering access to a service provided by a service provider to subscribers of at least one ISP, the method comprising the steps of:

said service provider maintaining a list of IP addresses assigned to said at least one ISP (inherent in ISP-column 5, lines 35-40); and when a user attempts to access said service through a computer having an IP address, said service enabling access if said IP address appears in said list ("access restrictions"-abstract; "authenticating the clients right to receive the requested resource"-column 3, lines 1-5)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/IL00/00496

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Claim 47 lacks novelty under PCT article 33(2) as being anticipated by ROSENBLIT, M. "Secure Software Distribution". IEEE, Proc. Of NOMS '94.

Per independent claim 47; ROSENBLIT discloses a method of payment for a software product, the method comprising the following steps:

invoking a payment process during installation by a user of said software product on a customer computer station that is connectable to a network; and

completing said installation only if said user has successfully completed said payment process (""No software activation without licensing"-page 494; "vendor"-page 494), wherein said payment process comprises the following steps:

establishing a connection from said customer computer station to a transaction service via a network service provider;

receiving, by said network service provider, customer identity information from said customer computer station ("users digital signature"-page 496); and

sending, by said transaction service, authorization to said customer computer station ("software keys"-page 494).

Claim 47 lacks novelty under PCT article 33(2) as being anticipated by CHENG et al., EP 811,942 A2, published 10 December 1997.

Per independent claim 47, CHENG et al. method of payment for a software product, the method comprising the following steps:

invoking a payment process during installation by a user of said software product on a customer computer station that is connectable to a network "electronic payment by the user to the software vendor"-page 3, lines 49-51); and completing said installation only if said user has successfully completed said payment process ("authentication"-abstract), wherein said payment process comprises the following steps:

establishing a connection from said customer computer station to a transaction service via a network service provider ("service provider"-abstract);

receiving, by said network service provider, customer identity information from said customer computer station ("information identifying the client computers and the software products stored thereon"-abstract); and

sending, by said transaction service, authorization to said customer computer station ("Authentication of the user ensures only registered users obtain software updates"-abstract).

Claim 3-4, 6-8 , 40, 46 and 54 are lack inventive step under PCT article 33(3) as being obvious over EGENDORF , WO 97/03410 A1, published 30 January 1997.

Per dependent claims 3-4 , EIGENDORF further discloses: wherein the-customer identity information comprises caller identification information (inherent in "phone bill"-page 5, lines 10-19; "modem over a network to the providers equipment"-page 2, lines 5-8).

It is noted the Automatic Number Identification (ANI) *does not appear to be* claimed. In the interest of "compact prosecution"; it is noted that MELEN et al. taught automatically linking a caller line identification with an on-line transaction (page 9, line 13 to page 10, line 2; page 12, lines 17-23; page 14, lines 1-10; page 17, lines 9-17; page 16, line 12 to page 17, line 8).

It would have been obvious to a Person Having Ordinary Skill In The Art, *i.e.*, *PHOSITA*, at the time of the invention to employ the ANI method of MELEN in EGENDORF in order to increase the level of security of EGENDORF, by providing an additional information that would have been difficult to spoof.

Per dependent claim 54, claimed password was *implicit* in the EGENDORF since using a password to log on to an ISP was ubiquitous, and not doing so with EGENDORF would have left the system open to serious security breaches. Therefore, it would have been obvious to *PHOSITA* at the time of the invention to include a password in the ISP log on of EGENDORF in order to prevent security breached in EGENDORF and in order to educe fraud

Per dependent claim 6; EGENDORF fails to discloses: the method further comprising the step of obtaining a customer's IP address from an HTTP "Forwarded-For" header. However, Official Notice is taken that it was notoriously well-known in the art at the time of the invention to obtain an IP address from the "forwarded from" header. It would have been obvious to *PHOSITA* at the time of the invention to employ this well-known technique in EGENDORF in order to implement and otherwise efficiently obtaining the Internet address of EGENDORF from the transactional information as suggested by EGENDORF (col. 5, lines 30-35).

Per dependent claim 7, and 8; EGENDORF fails to disclose obtaining the IP address from a background service. However, "Official Notice" is hereby taken that it was well-known in the art at the time of the invention to obtain an IP address in the background. It would have been obvious to *PHOSITA* at the time of the invention to obtain an IP address in the background by requesting a direct connection to a server in order to expand the method of EGENDORF to accommodate customers linking through proxy servers that shielded IP information, and thus expand the customer base of EGENDORF.

Per dependent claim 40, the sum total of these claim limitations amounts to matching a customer in a database without necessarily having 100% of the information exactly perfect. This is a notoriously well-known technique, because human beings were known to make slight variations in inputting customer data. It would have been obvious to *PHOSITA* at the time of the invention to find a "best match" of a customer, rather than an exact match, to allow for slight amounts of variations in customer inputted data, and thus in order to make the system tolerant of slight variations in human inputted data, and thus to significantly reduce the likelihood of multiple entries for the same individual customer in the transaction databases of the vendors of EGENDORF.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Per dependent claim 46, "Official Notice" is hereby taken that it was notoriously well-known in the art to credit a users account for returns and overcharges. For example, it was known to contact a credit card company and inform them of an overcharge. It would have been obvious to *PHOSITA* at the time of the invention to credit the account of EGENDORF in case of an overcharge, in order to satisfy the customer and user of EGENDORF.

Per dependent claim 54, it was known to use a password to authenticate a user. It would have been obvious to *PHOSITA* at the time of the invention to employ a password in EGENDORF in order to increase the security of the authentication system of EGENDORF.

Claim 9 lacks inventive step under PCT article 33(3) as being obvious over EGENDORF , WO 97/03410 A1, published 30 January 1997; in view of BLUMENEAL, WO 98/10349, published 12 March 1998 .

Per dependent claim 9; EGENDORF lacks an explicit recitation of obtaining IP information by downloading an application program. However, BLUMNEAU, on the other hand, demonstrates that it was notoriously well-known to employ a JAVA applet to obtain an IP address of a specific user(abstract, page 12, line 8 to page 17, line 27 and page 31, lines 9-34). It would have been obvious to *PHOSITA* at the time of the invention to employ a JAVA™ applet, such as on of the type described by BLUMNEAU, to obtain the IP address of EGENDORF in order to verify the IP address given by the ISP of BLUMNEAU and thus in order to provide enhanced security (as a double check of the information provided by BLUMENEAU), in order to decrease the risk of fraud.

Claim 41, lacks inventive step under PCT article 33(3) as being obvious over MELEN et al. WO 97/29584 A1, published 14 August 1997.

Per dependent claim 41, the sum total of these claim limitations amounts to matching a customer in a database without necessarily having 100% of the information exactly perfect. This is a notoriously well-known technique, because human beings were known to make slight variations in inputting customer data. It would have been obvious to *PHOSITA* at the time of the invention to find a "best match" of a customer, rather than an exact match, to allow for slight amounts of variations in customer inputted data, and thus in order to make the system tolerant of slight variations in human inputted data, and thus to significantly reduce the likelihood of multiple entries for the same individual customer in the transaction databases of the vendors of MELEN et al.

Claim 35-38 lack inventive step under PCT article 33(3) as being obvious over NIEMINEN et al, EP 924,630 A1, published 23 June 1999; in view of HEIZBERG, L., "Every Educator's WWW: the World Wide Web - Explained at Last without Hype", Electronic Learning, v. 15, n. 2, p. 48, published October 1995..

Per independent claim 35, NIEMINEN et al. discloses method for obtaining an IP address of a computer having a browser configured to use a proxy server for selected services and configured not to use a proxy server for other services, the method comprising the steps of:

instructing said browser to open a connection to one of said other services ("delivering the resource message from the proxy to the content server"-column 2, lines 5-7); and obtaining said IP address from said connection ("authenticating the right to receive the resource, and subsequently downloading the resource from the content server to the client"-column 2, lines 1-7; "ISB attempts to identify the client attempts to identify the client by identifying his terminal means. This can be done if the connection is initiated from a known source"-column 5, lines 25-37). The identification of the IP address from the connection to a server other than the proxy is *suggested only* (*i.e.*, not *explicit*) in the recited teaching of NIEMINEN et al.

Nonetheless, HEIZBERG, on the other hand, explicitly demonstrates that it was known to obtain the IP address from IP transactions ("Messages between computers are divided into multiple packets of data with the sending and receiving IP address as part of each packet"-page 3 of reprint). It would have been obvious to *PHOSITA* at the time of the invention to combine the obtaining step in the content server of NIEMEN et al. in order to properly route the TCPIP packets of NIEMINEN et al.

Per independent claim 35, NIEMINEN et al. discloses: a method for obtaining an IP address of a computer having a browser configured to use a proxy server for selected hosts and configured not to use a proxy server for other hosts, the method comprising the steps of:

instructing said browser to open a connection to one of said other hosts services ("delivering the resource message from the proxy to the content server"-column 2, lines 5-7); and obtaining said IP address from said connection ("authenticating the right to receive the resource, and subsequently downloading the resource from the content server to the client"-column 2, lines 1-7; "ISB attempts to identify the client attempts to identify the client by identifying his terminal means. This can be done if the connection is initiated from a known source"-column 5, lines 25-37). The identification of the IP address from the connection to a server other than the proxy is *suggested only* (*i.e.*, not *explicit*) in the recited teaching of NIEMINEN et al.

Nonetheless, HEIZBERG, on the other hand, explicitly demonstrates that it was known to obtain the IP address from IP transactions ("Messages between computers are divided into multiple packets of data with the sending and receiving IP address as part of each packet"-page 3 of reprint). It would have been obvious to *PHOSITA* at the time of the invention to combine the obtaining step in the content server of NIEMEN et al. in order to properly route the TCPIP packets of NIEMINEN et al..

Per independent claim 37; HEIZBERG discloses method for obtaining an IP address of a computer, the method comprising the step of: activating an application ("browser"-page 1) on said computer, wherein said application opens a connection to a server and said connection contains said IP address ("Messages between computers are divided into multiple packets of data with the sending and receiving IP address as part of each packet"-page 3 of reprint).

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Per dependent claim 38, it was notoriously well-known to download web browsers. It would have been obvious to *PHOSITA* at the time of the invention to download the browser of HEIZBERG in order to distribute it.

Claim 40 lack inventive step under PCT article 33(3) as being obvious over EGENDORF , WO 97/03410 A1, published 30 January 1997; in view of HUGUES et al., US 5,754,655 A, published 19 May 1998.

Per dependent claim 40, EGENDORF, lacks an explicit recitation of matching a plurality of information to determine if a transaction is approved, although it is implied. HUGUES et al., on the other hand, explicitly demonstrates matching a plurality of identifiers in a transaction (e.g., column 6, lines 15-45)with a database ("request authorization"-step 182-FIG. 5B) to approve a transaction. The claimed statistical significance (e.g. 100%) is inherent in this teaching. It would have been obvious to *PHOSITA* at the time of the invention to verify the identifiers of EGENDORF with a database in its approval process in order to insure that the buyer was indeed who he claimed to be.

Claim 41 lacks inventive step under PCT article 33(3) as being obvious over in view of MELEN et al. WO 97/29584 A1, published 14 August 1997; in view of HUGUES et al., US 5,754,655 A, published 19 May 1998.

Per dependent claim 41 MELEN lacks an explicit recitation of matching a plurality of information to determine if a transaction is approved, although it is implied. HUGUES et al., on the other hand, explicitly demonstrates matching a plurality of identifiers in a transaction (e.g., column 6, lines 15-45)with a database ("request authorization"-step 182-FIG. 5B) to approve a transaction. The claimed statistical significance (*e.g.* 100% match) is understood as *inherent* in this teaching, because it would not have worked as described otherwise. It would have been obvious to *PHOSITA* at the time of the invention to verify the identifiers of EGENDORF with a database in its approval process in order to insure that the buyer was indeed who he claimed to be.

Claim 42-43 lacks inventive step under PCT article 33(3) as being obvious over WILF et al., WO 99/08218 A1, published 18 February1999. in view of HUGUES et al., US 5,754,655 A, published 19 May 1998.

Per dependent claims 42-43 WILF et al. lacks an explicit recitation of matching a plurality of information to determine if a transaction is approved, although it is implied. HUGUES et al., on the other hand, explicitly demonstrates matching a plurality of identifiers in a transaction (e.g., column 6, lines 15-45) with a database ("request authorization"-step 182-FIG. 5B) to approve a transaction. The claimed statistical significance (e.g. 100%) is understood as *inherent* in this teaching. It would have been obvious to *PHOSITA* at the time of the invention to verify the identifiers of EGENDORF with a database in its approval process in order to insure that the buyer was indeed who he claimed to be.

Claims 48-51 lack inventive step under PCT article 33(3) as being obvious over Anonymous, *Mmwire* "PC Game Rental Provider Looks to IPO In a Year", *mmWire*, vol. 6, no. 115, 06/1999; in view of MELEN et al. WO 97/29584 A1, published 14 August 1997.

Per independent claim 48, *mmWire* discloses a method of payment for a software product installed on a customer computer station that is connectable to a network, the method comprising the following steps:

invoking a payment process at least a predetermined period of time after installation by a user of said software product on said customer computer station ("Upon installation, renters are prompted to send registration and payment information by the internet"-page 1; and

enabling subsequent use of said software product only if said user has successfully completed said payment process, wherein said payment process comprises the following steps:

establishing a connection from said customer computer station to a transaction service via a network service provider (inherent in "Information via the internet"-page 1).

MmWire lacks receiving the identity information via the ISP.

MELEN et al., on the other hand, demonstrates obtaining billing information from an ISP (abstract, page 5, lines 18-21, page 7, lines 1-5, page 11, lines 32-page 12, line 7). It would have been obvious to *PHOSITA* at the time of the invention to employ an ISP to bill the software rental of *MmWire* in order to increase to numbers of articles and serves available by the billing method of MELEN et al.

receiving, by said network service provider, customer identity information from said customer computer station; and

sending, by said transaction service, authorization to said customer computer station.

Per independent claim 49, this is given a negative opinion on substantially identical grounds to independent claim 48.

Per dependent claim 50-51, it was known to prompt payment for software after a preset time/ and number of times used. It would have been obvious to *PHOSITA* a the time of the invention to charge the user of *mmWire* and MELEN et al. in order to allow the user a free trial of the software of the device.

Per independent claims 44-45, the entire set of claimed steps *in combination* was not uncovered in the prior art of record.

Per independent claim 1-34 and 36; PAYNE et al. demonstrates a generic network sales system (abstract). This is cumulative to the references explicitly applied to these claims above.

Per claims 20-34 and 42-43, ANONYMOUS "VeriFone and Portal To Deliver Integrated Payment and Billing" demonstrates that is was known to provide payment services to ISPS in order to allow ISPs to deliver more products and services. This reference is cumulative to the art *explicitly* applied to these claims above.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

NEW CITATIONS

WO 97/29584 A1 (MELEN et al.) 14 August 1997, see page 5, lines 19-23, page 6, lines 19-23, page 7, lines 1-7, page 9, lines 4-15, page 10, lines 4-11, and page 11, lines 14-18.

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